

Security of Computers

WHEN, if ever, should the claims of society override the claims of an individual to his privacy? This is the question which has had a great deal of publicity recently, first with the refusal of a group of British medical doctors to register the names of some of their patients at a central data bank and then late last week with the publication of the government white paper on the security of the census (HMSO, Cmnd 5365, £0.21).

No one will deny that all attempts should be made to protect a person's privacy but is it at all possible to live in a modern sophisticated society without some infringement upon a person's private life?

In this respect there is no doubt that the scourge of those who seek the ultimate in privacy is the computer. There cannot be many people whose names are not recorded on the peripheral equipment of some computer or other. Even Mr Howard Hughes, who values his privacy highly and who, according to rumour, is now living, if that is the word, in London, has more to fear from the faceless computer than from the cameramen ready to record his movements if he ever appears in public.

But censuses are the prime example of the invasion of privacy in order to obtain information which will enable the quality of life to be improved and society, in general, to benefit. The worry expressed after the 1971 census in Britain was that the information provided by householders up and down the country would be put to use other than that for which it was first intended. The white paper at least effectively quashes such rumours and the recommendations of the Royal Statistical Society, which was asked to report on the security of information provided by the 1971 census, would, if implemented, do a great deal to ensure a much greater degree of confidentiality of the next census. The government, however, argues quite convincingly that even though the census information demands a high degree of confidentiality, which it already receives, the introduction of additional security measures to deal with small additional risks would not be justified if the costs involved in doing so were disproportionate to the costs of the entire operation. And this is the nub of the entire matter. The government can be guaranteed to preserve to the best of its abilities the confidentiality of the census information but can the same thing be said of other kinds of data stored in computers not necessarily operated by government departments? Absolute security, such as accorded the crown jewels, is not a practical proposition with information stored for use on a computer. But the question must be asked whether in the long run the crown jewels or the rights of people to confidentiality of their own affairs are most important.

But the benefits of using computers in today's society greatly outweigh the disadvantages, worrying though these

may be to some. To medical doctors the advantages of having a national or even a regional data centre, in which would be listed, for example, the names of people who have rare blood groups, or those who are allergic to particular drugs, or indeed the names of people who are prepared to donate organs in the event of their deaths, would be a boon that would save lives. But although such organization would seem sensible and perhaps inevitable in the long run, a great deal of confidence will have to be developed in the security of computers before it happens for it is patently obvious that if such information as this fell into the wrong hands it could be dangerous. The British Computer Society, however, has produced guidelines for the safe use of computers but in spite of all its goodwill it has not as yet persuaded the public that it is serious about its intentions. Such confidence should develop in the years to come but it will not be a rapid process. Rather, there will be a slow realization that data stored in computers run by reputable organizations are safe.

Sir Thomas More in 1516 envisaged an imaginary island where the ideal form of society existed. It would indeed be fascinating to know whether Sir Thomas, if he had lived some 450 years later, would have seen a place for computers in his Utopia.

100 Years Ago



The Pay of Scientific Men

It is unfortunately too true, as stated in your last week's leading article, that whether the claims of men of Science in serving their country are generally acknowledged in the future must to a large extent depend upon the men of Science themselves. I say unfortunately because, as a general rule, such claims, at least as far as pecuniary rewards go, could not be left in worse hands. I know so well how utterly repugnant it is to the feelings of all true and earnest workers in Science even to speak of such matters, however much they may be compelled to feel them sometimes, that they will be the last to force public attention to the question. Though this may be a natural and honourable feeling as far as each individual is concerned, I cannot help thinking that it is one which for the sake of the Science they love, it is a duty to place, for the time at least, in abeyance.

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OLD WORLD

Select Committee Renews its Battle over Computers

IN spite of recent financial aid given to International Computers Limited by the government, the Select Committee on Science and Technology is far from satisfied that the government is doing all it can to foster the industry in Britain. Earlier this week Mr Airey Neave, chairman of the select committee, introduced his committee's latest report which consists of an analysis of the progress made by the government, or should it be said lack of progress, in implementing the recommendations made by the select committee in its report on the British computer industry which was published in November 1971. (*Second Report on the UK Computer Industry* (First Part) HMSO, £0.185 and see *Nature*, **234**, 117; 1971).

The select committee is still convinced that Britain should develop a strong national computer industry whether or not closer association with computer interests in other European countries will eventually arise. According to Mr Neave, Britain should remain in the "big league" of computer manufacturers and to achieve this the government should aid the industry in Britain to the tune of £50 million per year. The government money which has already been assigned to the computer industry in Britain amounts to a little over £12 million a year for the next 3 years. Most of this money is a loan which will eventually have to be repaid. This is both unsatisfactory and inadequate according to the select committee.

In 1971 the select committee argued most persuasively for the setting up of a computer research and development board through which all government support for the industry should be channelled. The government's answer to this recommendation is the requirements board for Computers, Systems and Electronics set up last October within the Department of Trade and Industry. This the select committee also considers to be inadequate. Mr Neave emphasized on Tuesday that the board has, so far, made little impact on the major computer manufacturers although he still hoped that it would eventually carry out "a substantial part of the recommendations" made in the previous report. Mr Neave, however, does not hold out very much hope for this, for the limited character of the board is "in no doubt due in part to the government's failure to accept the committee's views on the appropriate size and method for the support of the industry."

The select committee again in this

report emphasizes that a long term policy for computing in Britain should be formulated. But it is highly unlikely that the government will accede to the committee's request. Last summer when the select committee suggested in its report on research and development that a national research and development policy be formulated the government shunned the idea (see *Nature*, **237**, 63; 1972). The British Government is firmly wedded to the idea that national policy on research and development should develop out of the policies of the individual departments and it would be most out of character if the government decided that a national policy for computers would be in order.

One of the most sensitive of the recommendations made by the select committee in 1971 was that the government policy of single tendering as a means of giving preferential support to the British industry be discontinued in favour of a block grant in-aid to the industry but the committee notes, with regret, in its present report, that the policy of single tendering still continues. "We have not heard any convincing evidence in support of the method of single tender preference which the government continues to use". This practice is bad for the industry and the user, continues the select committee, and it calls most strongly for

the minister, Mr Christopher Chataway, to reconsider.

The present report is the first of two that the select committee plans to publish on the computer industry. The second report, which Mr Neave said should be published within a few months, will concentrate on the action taken by the government in promoting international collaboration. A flavour of this report is given in the present publication where the select committee points out that whereas it commends the interest shown by the Department of Trade and Industry in ICL's future, it is perturbed by the extent of the government's direct concern with the formulation of international policy within the company. But some of the select committee's plans for the second report have been thwarted, as previously reported in *Nature* (**244**, 3; 1973), by the refusal of the commissioners of the European Economic Commission to give public evidence to a select committee of a national parliament. The refusal is probably not based on any policy for the future of the computer industry in Europe but rather on the fear that nine national parliaments would demand the rights publicly to interview the commissioners. In spite of this setback, Mr Neave said that the select committee should be visiting Brussels in September.

RESEARCH AND DEVELOPMENT

Accounting for a decade

EXPENDITURE on research and development in Britain in the natural and medical sciences and engineering rose from £658 million in 1961-62 to £1,082 million in 1969-70. But expenditure as a percentage of gross domestic product remained constant at between 2.7 and 2.8%.

These figures emerge from a survey carried out by the Central Statistical Office which was published last week (*Research and Development Expenditure*, HMSO, £1.55). Amongst the welter of figures, which are not corrected for inflation, it is revealed that expenditure on defence research and development fell by almost half during the decade, while expenditure on the civil side rose correspondingly. In 1961-62 defence expenditure made up 1.02% of the British gross domestic product, while civil research and development expenditure accounted for

1.70%. By 1970 defence spending was reduced to 0.57%, whereas outlay on other research and development rose to 2.22%.

The government's contribution to research and development fell during the decade from 57.5% of the total in 1961 to 51.7% by 1970, the remainder being provided by public corporations, private industry, the universities (with other than money from the research councils) and overseas expenditure. During the decade the public corporations' contribution to research and development expenditure rose from 3.5% to about 4.5%, whereas private industry provided between 37 and 39% of research and development finance.

Current expenditure tended to rise faster during the 1960s than capital outlay, with capital expenditure amounting to £105 million during 1966-67 and current expenditure amounting to £797 million. In 1969-70 capital expenditure had reached £120 million, but current expenditure had increased to £946 million.

SPACE

Same Old Story

LAST week's performance by the European nations at the European Space Conference ran true to form with nobody agreeing with anybody else. As a result no decisions were taken, the ministers returned home to think things over, and the circus will get under way again on July 31.

The postponing of decisions until then makes timing for the Spacelab programme rather tight. The European Space Research Organization has until August 15 to let NASA know whether or not it is going to participate in the post-Apollo programme by building Spacelab. Originally the ESRO council was to formally take its decision on July 31, after last week's space conference, but now that the ESC is meeting on that day, ESRO has put back its meeting to August 1. But any failure to agree on July 31 must seriously jeopardize the possibility of Europe meeting the August 15 deadline.

Last week's problems were merely a continuation of the old troubles. Britain does not want to build launchers, but France does; Germany wants to build Spacelab, but not a maritime satellite, which is currently Britain's favourite project. The situation was further complicated by several of the other European nations sending their ministers to the eleven member conference without clear mandates on what projects to support. Hopefully everyone will have decided where they stand by the end of the month.

Meanwhile ESRO has run into a headwind with its plans for Aerosat. ESRO was hoping shortly to initial a memorandum of understanding with the United States Administration which would have set up a joint Aeronautical Satellite Evaluation Programme between the European nations, the United States and Canada. The programme would have examined the possibilities of controlling air traffic by satellite—a problem that is becoming increasingly urgent as the number of flights over the Atlantic and Pacific mount (800 flights a day are projected for the north Atlantic by 1980). The airlines in the United States, however, are having doubts about the programme—possibly because they are not too certain they want to pay if it is finally decided to go ahead. As a result, although no official word has come from the USA, it has become plain that the United States Administration may not be able to sign the agreement as it stands. ESRO has therefore postponed the choice of an industrial partner in the United States. If all had gone well, ESRO would have chosen between five United States aerospace companies who were to have been full partners in

the development of the space segment of the aerospace programme—the building of the satellites and associated launch and control facilities.

So worried is ESRO by the prospect of the United States not signing that it has decided to examine the possibilities open to it if the United States does back out. Cooperation with Canada, and later Japan and Australia, is still very much on the cards, and ESRO is to examine the possibilities of using an adapted version of the Orbital Test Satellite as the basis for an aeronautical satellite. Clearly the intention is to put some pressure on the United States Administration from the European end, to balance the pressure that the airlines are currently exerting.

POLAND

Ten Year Plans

from a Correspondent

THE Second Polish Scientific Congress, which met recently in Warsaw, had as its theme "Science in the service of the community" and was devoted, essentially, to the planning of research and expansion for the next decade or more. Held, auspiciously, in a year which commemorates not only the 500th Anniversary of the birth of Copernicus, but also the bi-centenary of the Polish Educational Commission and the centenary of the foundation (in Cracow) of the Polish Academy of Sciences, the Conference was attended by more than 2,000 delegates, some 900 of whom came from the Warsaw area.

Outlining the development of Polish science since the first congress, twenty years ago, the President of the Polish Academy of Sciences, Academician Włodzimierz Trzebiatowski noted that Poland now has more than 350 scientific research institutes, design bureaux and laboratories, and that the number of senior qualified personnel is now 260,000. He placed special emphasis, in accordance with current COMECON policy, on the role of scientists and scientific institutions in "accelerating scientific and technological progress".

Among the individual speeches, outlining plans for the coming decade, Professor Dionizy Smoleński, vice-president of the Academy, indicated that in the exact sciences, a basis of research "integrally linked" with the over-all economic development of the country has now been established, and that special emphasis should be placed on developing such fields as cryoelectronics, plasma physics, laser technology and information processing techniques. For the biological sciences, Professor Bohdan Dobrański stressed the need for increased concentration on molecular, environmental and evolutionary biology.

REACTORS

Gas Breeder Moves

REACTOR designers in both Europe and the United States are pushing ahead with plans for a gas-cooled fast breeder reactor (GFBR). At a meeting of interested parties in London last week, convened by the British Nuclear Forum, the view was expressed that the better breeding capabilities of the GFBR make it particularly attractive when linked with the High Temperature Reactor (HTR) and in discussions it was generally accepted that the GFBR also offers a high degree of safety.

In Europe the running as far as GFBRs are concerned has been made by the Nuclear Energy Agency of the Organization for Economic Cooperation and Development and by the Gas Breeder Reactor Association (GBRA), which represents those parts of industry with an interest in GFBRs. In the long term the GBRA aims to see the construction of a GFBR demonstration plant started in Europe before the end of the decade. So far the GBRA has spent £0.75 million through its study group in Brussels since it was set up in 1969. The NEA collaborative programme, on the other hand, involves the coordination of £5 million of work in government laboratories around Europe. In addition Kraftwerk Union is working independently on the GFBR with government aid.

The prime mover in the United States is Gulf General Atomic, which sees the GFBR as a natural partner for its HTRs. Dr P. Fortescue of Gulf spoke of the "symbiosis of fast and thermal reactors" and of a situation in which a fast breeder reactor would act as a fuel factory for an HTR, independent of external means of enrichment and supplying such materials as uranium-233. The fact that a helium coolant does not much modify the spectrum of neutrons within a reactor, by contrast with liquid sodium, makes the GFBR a better breeder than sodium-cooled reactors like the one at Dounreay and thus a more suitable partner for the HTR on economic grounds. The HTR has other advantages of its own, of course, in that it can produce process heat at a temperature of interest, for example, to steel-makers and the chemical industry. Gulf, supported by many interested utilities, has sunk about £6 million into the GFBR and although not committed to a particular year for starting on a demonstration plant it has a thirteen-year schedule drawn up for a 300 MW reactor system. It now seems possible that a GFBR will be chosen to follow the Westinghouse sodium-cooled reactor as the second nationally founded demonstration plant in the USA.

NEW WORLD

Future of Psychosurgery in Doubt

by our Washington Correspondent

LOUIS SMITH, a 36-year-old Michigan man, was offered a proposition last year which he found difficult to refuse. He had spent half his life committed to mental institutions as a criminal sexual psychopath and he was offered the chance to have an experimental operation on his brain which, if successful, would reduce his aggression and give him his freedom. He agreed to the operation, but before it could take place the whole matter hit the headlines, a court action was filed to stop it and the issue became an important test case. Last week, a special three-man panel of judges in Detroit handed down a decision on the matter which is likely to have a huge impact not only on the future of psychosurgery in the United States, but also on any biomedical research involving prisoners.

In essence, the court ruled that a person committed against his will to a mental institution is in no position to give his consent freely and voluntarily to psychosurgery, and, moreover, the present lack of knowledge about brain function and the effects of psychosurgery "makes a knowledgeable consent to psychosurgery literally impossible". The ruling has the effect of preventing the use of psychosurgery on anybody committed to institutions in the State of Michigan, but the decision will clearly be felt a long way from Detroit.

Ironically, however, one thing which is not affected by the ruling is the case which led to the court action in the first place. When the matter hit the headlines, the Michigan Department of Mental Health, which was sponsoring the project, withdrew the funding and earlier this year the same panel of judges directed that Mr Smith should be released. The statute under which he was committed was repealed in 1968, and the court decided that he was being held unconstitutionally; he had also been notably free from violence in the past few years, and the court was told that he posed no unreasonable danger to society and should be released.

Mr Smith was to have been the first patient in an experimental project at the Lafayette Clinic, a highly respected psychiatric research institute connected with Wayne State University (see *Nature*, **242**, 222; 1973). The objective was to compare the effects of surgery on the amygdala, a part of the brain associated with emotional responses, with the effects of cyproterone acetate, an experi-

mental drug developed in Germany which has some known side effects including causing impotence. The idea was to determine if either procedure could be used to control aggression and to provide permanent relief for the patient.

A form consenting to the psychosurgery operation was signed by Smith, and the project was reviewed by two committees to examine the scientific worthiness of the study and the validity of the consent. Both committees gave their approval, and electrodes were to be inserted into Smith's brain on January

15. The next step would have been to monitor the electrical activity of the amygdala, and if there were signs of abnormality a tiny portion of brain tissue would have been coagulated with an electric current.

The court ruled last week, however, that the proposed project was founded on dubious ethical and legal grounds. First, there is the question of informed consent. The judges decided that "informed consent cannot be given by an involuntarily detained mental patient for psychosurgery". For one thing, potential subjects for the experiment would

RESEARCH TRAINING

Give and Take

by our Washington Correspondent

THE Administration has juggled some money around in the budget of the Department of Health, Education and Welfare, and come up with \$30 million for a new programme of biomedical research training fellowships. The new programme will begin this year and will eventually replace the present training grant and fellowship programmes administered by the National Institutes of Health, which are due to be phased out over the next three years. It is also the Administration's answer to the barrage of criticism from the biomedical community that greeted the original plans to scrap NIH training programmes.

The new scheme represents a considerable retreat from the Administration's intention to kill biomedical research training programmes entirely, but the plans are unlikely to silence the critics. For one thing, when he announced the plan last week during a speech to the Interassembly Council of Scientists at NIH, Caspar Weinberger, Secretary of HEW, made clear that the \$30 million to be spent this year will come out of money that has already been budgeted for the old programme. In other words, the \$21 million cut in training and fellowship programmes at NIH is not being restored. And, although Weinberger said that funding for the new programme will reach \$90 million in three years time, even that will be some \$60 million less than NIH spent on research training grants and fellowships last year.

The scheme announced by Wein-

berger last week involves individual fellowships of \$10,000 each which will be given directly to scientists rather than to institutions. "The old programmes are being phased out", he said, "because only small amounts of money actually reached the research trainee, while the bulk went to institutions", which is somewhat different from the rationale that has been given in the past for scrapping the old programmes. The Administration usually argues that it is not the business of the federal government to support postdoctoral students, that the need for biomedical scientists is not likely to grow as quickly in the next few years as it has recently, and that postdoctoral students are likely to earn large salaries when they have completed training, so they should pay for their studies by taking loans.

Other provisions of the programme will be that the funds will be used only for scientists who already have an MD or a PhD, that each student can receive support for up to three years, and there will also be a paycheck provision "for those trainees who do not spend an appropriate length of time in research and teaching after completing training". So far, no definition of an appropriate length of time is available.

In the meantime, Congress is also acting to reinstate the training programmes. A bill was passed by the House of Representatives in May which would fund the programmes at about \$200 million a year, and last week Senator Kennedy's Senate Health subcommittee also passed a bill to set up new programmes. There are considerable differences between the two bills, however, and even if the Senate passes Kennedy's legislation in the next few weeks, it will take a conference committee until about September to reconcile the differences.

already have been institutionalized for a long time, their decisions would always have been made for them and their conception of their own physical and mental worth would have been greatly diminished during their commitment. All of those factors would reduce their capability to make rational decisions. Another barrier to informed consent, the judges suggested, is the fact that knowledge of brain function and of the effects of psychosurgery is sparse, to say the least, and that makes balancing of risks and benefits virtually impossible. Finally, and perhaps most important, the judges question whether a patient confined against his will in an institution can voluntarily give his consent to anything when his freedom may hang on his decision. "It is impossible for an involuntarily detained mental patient to be free of ulterior forms of restraint or coercion when his very release from the institution may depend on his cooperating with the institutional authorities and giving consent to experimental surgery", the judges assert.

Apart from those considerations, the court also ruled that the experiment would have violated the First Amendment to the US Constitution, which governs freedom of speech and ideas. The rationale for such a determination is that if the First Amendment protects the freedom to express ideas, it also protects the freedom to generate ideas. Psychosurgery, however, often blunts the emotions, deadens the memory, impairs the intellect and, consequently, it can limit the patient's ability to generate ideas. "To allow an involuntarily detained mental patient to consent to the type of psychosurgery proposed in this case, and to permit the State to perform it, would be to condone State action in violation of basic First Amendment rights of such patients", the court ruled.

What are the likely consequences of the court ruling? First, it is clear that unless the case is appealed, which at present seems unlikely, similar psychosurgery experiments on incarcerated mental patients in the United States would be quickly stopped. Less clear cut, however, is the possible effect on the practice of psychosurgery on private, free patients, because the decision hinges chiefly on the fact that the patients in this case are effectively denied freedom of choice through their incarceration. Nevertheless, the judges' opinion that the state of the art of brain research is such that there is insufficient knowledge to allow the balancing of risks and benefits seems to have broad application.

More far reaching is the possible impact of the decision on other types of biomedical research involving prisoners. It has been suggested that many of the court's arguments about the ability of an incarcerated person to give free and

informed consent apply to prisoners who agree to take part in drug trials. Mr Charles Halpern, an attorney with the Washington-based Center for Law and Social Policy, suggested last week, for example, that the ruling will lead to a much more cautious approach in prison research, and that drug companies will probably be forced to scrutinize much more closely the adequacy of their procedures for obtaining consent from prisoners who take part in drug trials.

As for the setting up of national policies, the court ruling is likely to add impetus to legislation pending before Congress which calls for a two-year moratorium on all psychosurgery. It is also likely to influence the deliberations of an Inter-Institute Work Group on Brain and Behavior, which has been set up in the National Institutes of Health, to examine various aspects of the problem. Clearly, the Detroit court has, in a tradition that is by now familiar in the US legal system, handed down a decision that has sweeping social implications. It is believed to be the first time, however, that a court has told scientists that they cannot go ahead with a particular experimental technique.

SOUTH AFRICA

NASA Bows Out

by our Washington Correspondent

THE National Aeronautics and Space Administration has begun to extricate itself from an embarrassing situation by announcing that it plans to close part of a tracking station near Johannesburg, South Africa, next year. And, provided it can be done without harming the space programme, NASA hopes to shut the station completely by the end of 1975.

The tracking station is being phased down, and possibly closed, ostensibly for technical and economic reasons — NASA officials say that it is no longer vital to the space programme—but an underlying motive is that it has become a rather visible thorn in the agency's flesh in the past few years. The problem is that the station, which is operated for NASA by the South African Council for Scientific and Industrial Research (CSIR), is run according to the doctrine of apartheid, and that fact has upset some members of Congress. They argue that although the station is being financed by the US government, it is being operated in violation of US domestic laws, namely the Civil Rights Act.

Charles C. Diggs, a Democrat from Detroit and chairman of the House Foreign Relations Subcommittee on Africa, has hauled NASA officials before his committee to explain why the station is necessary and why NASA has allowed it to be run on racial lines. And

Charles Rangel, a Democrat from Harlem, has twice tried unsuccessfully to delete funding for the station from NASA's budget.

NASA officials and their supporters in Congress have met these challenges with the argument that the station is vital to provide continuous tracking, particularly of planetary missions, and that as it is being operated by the South African government under contract it must conform to South African laws. The agency has, however, managed to wring a few concessions out of the CSIR, such as improved housing and medical care for the black workers at the installation, but, as Mr Ken Hechler, chairman of the subcommittee that oversees NASA's tracking operations, said in a recent debate in the House of Representatives, "the relative salaries of black and white personnel are shockingly unequal and inequitable".

In that same debate, Mr Olin Teague, of Texas, Chairman of the Committee on Science and Astronautics and NASA's chief supporter in the House, said that the "station in South Africa is one of the most important tracking stations we have". What, then has led to the rather abrupt reassessment of the station's importance? According to Mr Gerald Truszynski, head of NASA's Office of Tracking and Data Acquisition, the planned phase-down of the station was "actually a technical decision", but he added that "I will say this, if we didn't need that station in that location we would have been out before now."

The tracking station has two components, a Deep Space Network (DSN) facility for tracking planetary spacecraft, and a satellite tracking (STDN) facility for tracking unmanned Earth orbiting satellites. The total cost of the installation is about \$12.5 million, and running expenses are about \$2.5 million a year. It is the DSN which is being closed next year, and NASA is looking hard at the requirements for the STDN to see whether it can be closed a year later. The reason why the DSN is being closed is partly due to celestial mechanics: the trajectories of the planetary missions of the 1960s and the early 1970s were such that the spacecraft were visible only from the Southern Hemisphere for up to 100 days after they were launched, but the missions planned for the 1970s and early 1980s will be visible from NASA's facilities at Goldstone, California and Madrid.

In making the announcement of the plans to phase down the station last week, Dr James C. Fletcher, Administrator of NASA, said "NASA will always be grateful for the technical support and cooperation we have received from the Council for Scientific and Industrial Research and its dedicated station personnel".

NEWS AND VIEWS

Macrophage Electrophoretic Migration Test for Cancer

RECENT advances in our knowledge of immunology have influenced current attitudes to several aspects of neoplasia. There is now evidence that cells from both animal and human tumours differ antigenically from their corresponding normal counterparts—quantitatively and possibly qualitatively—and that these changes may evoke immune responses in the host (see, for example, *Nature*, **235**, 137; 1972).

In an attempt to develop reliable quantitative methods of measuring cell mediated immune reactions *in vitro*, Field and Caspary devised the macrophage electrophoretic mobility (MEM) test (*Lancet*, **2**, 1337; 1970, and *J. clin. Path.*, **24**, 179; 1971). In essence, the procedure depends sensitized peripheral blood lymphocytes reacting *in vitro* with the appropriate sensitizing antigen to produce and/or release a soluble principle which retards the electrophoretic migration of guinea-pig peritoneal macrophages; a cytopherometer is used to quantitate macrophage migration. The MEM test, which is reminiscent of procedures involving inhibition of macrophage migration, has been employed in studies of the mechanism of action of ALS and of lymphocyte sensitivity in neurological, thyroid and neoplastic disorders. Most recently, it has been proposed as a rapid and simple aid to the diagnosis of scrapie in sheep, an application that was briefly reported in last week's issue of *Nature* (**244**, 96; 1973).

Much interest and controversy has arisen from the results of MEM tests in patients with tumours. During an investigation of cell-mediated immune reactions to a basic protein from brain tissue, the encephalitogenetic factor (EF), Field and Caspary observed that sensitized lymphocytes occurred not only in patients with neurological damage but also and quite unexpectedly in all subjects with malignant tumours and not just those with carcinomatous neuropathy. Further studies by these workers have confirmed the initial observations and extended them to show that positive results occur in subjects who harbour tumours, irrespective of site or histogenesis as well as those who have had a malignant tumour removed and who are now clinically free of their disease.

Exceptions do occur and include patients with advanced metastatic disease or with lymphatic leukaemia. The anticipatory nature of this test is shown by positive results obtained in patients with *in situ* carcinoma of the cervix and up to nine years before the clinical appearance of a thyroid carcinoma.

The MEM test is, however, difficult because of technical problems (lymphocyte numbers, guinea-pig infection and cell selection in the cytopherometer) and has caused other workers to question its validity. But the independent confirmation by Pritchard and his colleagues (see, for example, *Brit. J. Cancer*, **27**, 1; 1973) of the results obtained from the MEM test, into which they have also introduced improvements with particular regard to sensitivity, must serve to dispel some of the doubts, and will almost certainly kindle the investigative zeal of some clinical oncologists.

There are at least three areas where more intensive investigation of the system is required. First, a detailed

clinical evaluation of the discriminatory capacity of the test has still to be carried out. Second, the nature of the tumour antigen or factor(s) accounting for lymphocyte sensitivity must be clarified. Finally, attempts are needed to evolve a modified system which could be prosecuted in sufficient numbers to be applied to routine clinical practice.

At present, the MEM test seems to represent a genuine early method of cancer detection, albeit without tumour localizing ability. But caution is still essential in interpreting the results in view of the variety of conditions already known to give false positive results in the "cancer" range; these include active tuberculosis, sarcoidosis, rheumatoid arthritis, disseminated lupus erythematosus, intrinsic asthma, influenzal infections and degenerative neurological disease. It is axiomatic, when studying methods of detecting neoplastic disorders, to include in all surveys many more patients with benign neoplasms and inflammatory and regenerative disorders; sufficient information along these lines is not yet available. The importance of adequate controls is well exemplified in the field of oncofoetal antigens. The carcinoembryonic antigen (CEA) was considered at one time to be specifically formed by endodermally-derived carcinomas but subsequent analyses have revealed elevated amounts of CEA or CEA-like materials in the blood of patients with non-endodermal tumours and several non-neoplastic conditions such as peptic ulceration, diverticulitis and cirrhosis. It is essential to examine the MEM test in pre-neoplastic conditions such as ulcerative colitis, in familial neoplasia (polyposis coli) and in diseases which enter into the differential diagnosis of malignant neoplasms such as chronic pancreatitis, diverticulitis and mammary gland dysplasia. If, after such a survey, the specificity of the test is confirmed, it would be outstandingly valuable in screening susceptible and "at risk" populations, provided also that it can be developed in such a way as to be routinely applicable to reasonable numbers of patients.

The second topic for more detailed study is the nature of the tumour antigen or factor responsible for sensitizing the host's lymphocytes. It is possible to obtain, from all the malignant tumours studied so far, a basic protein extract which is more effective than EF in retarding macrophages in the MEM test when applied to cases of malignant disease. As all malignant tumours examined to date gave positive MEM tests, it has been proposed that there may be a basic protein antigen common to all human malignancies; such material is presumably structurally related to, but not identical with, EF. Subsequent studies locate this antigenic activity to the plasma membrane of tumour cells and have failed to detect it in normal or hyperplastic tissues. It should be noted, however, that neither the EF nor the basic cancer protein extracts used in these studies were homogeneous by gel electrophoresis. There is thus room for doubt about the exact sensitizing agent. Could it, for instance, be a normal basic protein, such as a histone? Comparison of the analyses of EF by Caspary and Field (*Ann. N.Y. Acad. Sci.*, **122**, 182; 1965) and the histone F2A1 shows remarkable similarities and

at this time it is known that studies are in progress aimed at ascertaining if this or other histones could serve as potential antigens in the MEM test for lymphocytes from patients with cancer. Such a hypothesis is strengthened by the observation that the addition of nuclei or DNA to cancer basic protein extracts renders them ineffective in the test. Furthermore, histones are basic proteins whose properties enable them to interact with the known types of negatively charged groups on cell surfaces. It may be that those tumour cells which have an increased surface negative charge could bind histones to a greater extent than normal cells and in this way account for the location in excess of the activity in relation to the plasma membrane and thus possibly initiate an autoimmunization process.

In view of these doubts about the nature of the "antigens" used in the MEM test, it is prudent to interpret cautiously the significance of detecting scrapie-like antigens in ageing tissues as reported on page 174 of this issue of *Nature* and with such preliminary experimental data the conclusions regarding the role of the thymus in influencing changes in antigenic determinants on cells which may occur with age.

Finally, although there is some doubt about the nature of the antigen, this need not detract from the apparent clinical value of the MEM test. After all, the widely used Wassermann reaction does not employ the appropriate antigen. It is difficult, however, to envisage the present MEM test or the Cardiff modifications of it being used on a wide scale as only a few samples can be analysed each day. One way which might result in some improvement without loss of the anticipatory element might be attained if the nature of the factor produced and/or released by the lymphocytes to act on the macrophage was identified. It might then be possible to develop a radioimmunoassay for this "lymphocyte mediator" measuring its level *in vitro* after interaction of the "sensitized" lymphocytes and "tumour antigen".

If future work confirms the concept of an antigen common to or released by all human tumours and the ability to detect its presence at the pre-clinical stage of development, then this will almost certainly represent the genesis of a new era of oncological investigation. A. M. N.

PROTEIN STRUCTURE

Elusive Electrons

from our Molecular Biology Correspondent

So insatiable nowadays is the clamour for novelty in the trade at large that a new structure determination of a hydrolytic enzyme, an apocalyptic event not so long ago, would probably already stand an outsider's chance for the Yawn of the Year award. An area in which the crystallographers' efforts are, on the other hand, beginning to compel biochemists' attention is electron transfer. As Kraut and his colleagues now show (Salemme *et al.*, *J. biol. Chem.*, **248**, 3910; 1973), there is enough information in their new high-resolution structure of a bacterial *c*-type cytochrome to let the curly arrows fly. Ferricytochrome c_2 from the photosynthetic bacterium, *Rhodospirillum rubrum*, has a chain of 112 residues, with a close affinity, in terms of sequence and structure, to horse heart cytochrome *c*. The haem group, which is covalently linked to the protein, lies in a deep crevice, one edge only

projecting into the surrounding solvent. The walls of the crevice are made up mainly of hydrophobic side chains. Two thiol groups form covalent thioether bonds with the vinyl side chains of the haem, and one of the two external iron ligands is a histidine, the plane of its ring perpendicular to that of the haem, as expected. The ligand on the opposite side is, as in the eukaryotic cytochromes *c*, the sulphur of a methionine. Around the edges of the haem plane there are also the side chains of a serine, two tyrosines and a tryptophan, all so placed as to make hydrogen bonds with the haem propionyl groups.

Now a number of interesting inferences follow from the details of this structure. In the first place it seems to admit of little doubt about the site of its interaction with the membrane-bound bacteriochlorophyll, to which, when it is in the reduced state, it gives up an electron. Not only is a good part of the hydrophobic rim of the haem group exposed to the aqueous medium, with the polar propionyl side chains tucked into the essentially non-polar crevice, but the

Temperature Sensitive Elongation Factor Ts

BACTERIAL mutants with temperature sensitive enzymes have proved valuable tools in unravelling biological processes. Not least in studies of the mechanism of protein synthesis are such mutants playing an increasing role. Several mutants are now available to facilitate work on the function of tRNA in protein synthesis. The relevant proteins in this case are the elongation factors (EF) "G" and "T", the latter of which is composed of two components known as EFTu and EFTs. Temperature sensitive mutants of tRNA itself have been isolated before. Moreover, some time ago, temperature sensitive mutants of EFG were isolated in two different laboratories. A report from a member of one of these two laboratories, Kuwano, and his coworkers, in next week's issue of *Nature New Biology* suggests the availability of a temperature sensitive mutant of EFTs.

The *E. coli* mutant in question (HAK88) grows at elevated temperatures (42° C) only in the presence of added tRNA, similar in this requirement to the temperature sensitive tRNA containing mutants. The lesion, however, does not seem to be in the tRNA, for S100 from which tRNA has been removed exhibits the original temperature dependence, whereas both the extracted tRNA and the aminoacyl synthetases appear to be normal. S100 extracts from another mutant, containing a temperature sensitive EFG, complement the defective system, eliminating EFG as the responsible agent.

Restoration of protein synthesis *in vivo* by tRNA might be more likely if EFTs rather than EFTu were the defective factor. Whereas EFTu forms a stable complex with tRNA, Ts seems mainly to enhance the interaction of tRNA with EFTu.

First, at 0°, EFTs, whether from HAK88 or the parent strain HAK8, promotes the binding of GDP to EFTu and a strong EFTs concentration dependence of this binding is observed. EFTu, though itself readily inactivated by heating in the absence of GDP, is not more so when isolated from HAK88 instead of HAK8. The stimulation of GDP binding to EFTu, however, is significantly more temperature sensitive in the critical range, 36–42° C, when EFTs is taken from the mutant strain than when it is taken from the parent. Elegant confirmation of the identity of the defective protein in mutant HAK88 comes from work with the replicase of Q β -infected cells. It is known that two of the four polypeptide chains of Q β replicase are identical to EFTu and EFTs. When Q β replicase is isolated from HAK88, unlike the parent strain, RNA synthesis *in vitro* exhibits the temperature dependency one would predict if it contained the sensitive EFT factor.

E. coli HAK88 grown at 42° C does not synthesize RNA. Kuwano *et al.* suggest that there may be a common function of EFTs in its interactions with tRNA and in the hypothetical control of RNA synthesis both in normal and in virus-infected cells.

lips of the crevice are made up of a mass of lysine residues (eleven of the seventeen present in the molecule). Because the electron transfer would most simply occur by way of a direct interaction between the ferrous haem and an acceptor, this at once suggests a model whereby the phenophytin stacks onto the projecting edge of the haem, while the head groups of its associated phospholipids make favourable contact with the strongly positive protein surface. No doubt a more complex route could be contrived, but the mechanism that Salemme *et al.* suggest has the ring of persuasive simplicity.

A further striking feature that comes to light at 2 Å resolution is the disposition of the haem ligands: whereas the imidazole makes a right-angle with the haem plane, that is to say is collinear with one of the *d*-orbitals of the iron, the sulphur-iron bond on the distal side is conspicuously bent, the sulphur being a half Å off-axis. Three reasons can be envisaged: the methionine might be constrained by the geometry of its neighbours in the chain; of this, however, there is no indication, and instead the slightly blurred electron density in this region makes it appear that there is even some flexibility. Second, the position of the sulphur atom could be determined by a hydrogen bond to a tyrosine hydroxyl lying only 3 Å away, but this, the authors suggest, is rendered improbable by the partial positive charge which the sulphur must bear by virtue of its interaction with the iron, and which would militate against an energetically desirable hydrogen bond to the phenolic hydroxyl. This leaves the possibility of an electrostatic interaction between the partially positive sulphur atom and the appreciably negative phenolic oxygen. Salemme *et al.* have made this interaction the cornerstone of a plausible theory of electron transfer. A simple interpretation of extraneous (NMR) evidence on mammalian cytochrome *c* leads to the inference that one lobe of the iron orbital associated with the bulk of the unpaired spin density points towards the mouth of the crevice. Also in its immediate vicinity is a serine hydroxyl, which is the beginning of a chain of interactions, in that it makes a hydrogen bond to a phenolic hydroxyl hydrogen, the oxygen of which bonds to another phenolic hydroxyl, this time the one implicated in the interaction with the sulphur ligand. The reduction of the haem by an electron passed through the mouth of the crevice would then be assisted by a proton transfer to the serine from a suitable donor. This would induce a reversal of electron acceptor and donor roles in the hydrogen bond cascade, such as to destabilize the ferric state of the iron. The change of the charge on the iron would then eliminate the induced charge on the sulphur

ligand and in consequence its interaction with the phenolic oxygen. This hypothetical scheme leads to the prediction that in the reduced state the sulphur-iron bond will be unconstrained, and will lie perpendicular to the haem plane, and this a difference-Fourier examination of the reduced cytochrome, which is isomorphous with the oxidized form, it is hoped, will shortly reveal.

Ferredoxin is an electron transport protein of a quite different kind, which contains clustered iron and sulphur, instead of haem. Plant ferredoxins have a molecular weight of 12,000 and two iron atoms, whereas the bacterial ferredoxins have a molecular weight of 6,000—which puts them among the smallest known globular proteins—but pack more reductive punch, with eight iron atoms and eight corresponding labile sulphurs. Jensen and his colleagues have been working over these highly specialized and intriguing proteins, and now have the structure of *Micrococcus aerogenes* ferredoxin to 2 Å (Adman, Sieker and Jensen, *ibid.*, 3987). Being so short, the chain suffices only to form an exiguous shell around the redox centres, of which there are two, with no appreciable helical or other regular structure. There are two iron and sulphur clusters, which take the form of somewhat distorted cubes, the iron and sulphur atoms alternating at their corners. There is a striking approximate two-fold symmetry in the molecule, one redox cluster involving three cysteines from the N-terminal half of the chain and one from the C-terminal, and the other contrariwise. Tyrosine sits on either cluster and is presumably involved in electron transport.

NATURE CONSERVATION

Elephants and Man

from our Animal Ecology Correspondent

THE density of elephants in Ceylon is between five and twenty times lower than it is in African game reserves. This is not because the Ceylonese habitat is any less favourable but that intensification and development of agriculture in Africa has gone on apace and frequently without much planning. Utilization of savanna and scrub for farming has forced the elephant populations into over-small reserves. Crowding, coupled with an increased incidence of man-made fires and suppression of poaching, has precipitated critical situations in several places such as Tsavo and Murchison Falls (Laws, *Oikos*, 21, 1; 1970; Laws, Parker and Johnstone, *E. Afr. Wildl. J.*, 8, 163; 1970).

In a thorough and detailed study of the ecology and behaviour of *Elephas maximus* in Ceylon, McKay now reveals some of the differences in elephant ecology between Ceylon and Africa and

suggests a few measures that must be implemented if the *status quo* of elephants and agriculture is to be maintained (*Smithson. Contr. Zool.*, No. 125; 1973). In one important respect Ceylon is much more fortunate than Africa. Her agriculture is only now beginning to expand and demand more land, and at present, in the south-eastern quarter of the island at least, it is localized in the coastal strip. If such demands are met in a thoughtful fashion, a healthy population of elephants should be able to co-exist with a healthy food industry. This compromise would not only gladden the hearts of ecologists, conservationists and the like, but probably benefit the coffers of the tourist department as well. In the event, this latter may prove to be the key to implementation of action.

For much of the year elephants stay within the forests and scrubland and do not interfere with planted crops. During the wet season there is sufficient food available within the herd's home range and the various subgroups composing the herd lead a remarkably restricted life. Trouble comes in the dry season when the herds are forced to migrate in search of food. At present in Gal Oya National Park the biomass density of elephants is about 405 kg/km². This is about half of the total wild herbivore biomass (which is between 808 and 886 kg/km²). Each year the elephant population in the park eats about 10,500 kg/km², and it seems that this amount, coupled with what the other wild herbivores eat, is about the maximum the vegetation can stand. A lesson to be learnt from the African experience is that on no account should grazing of domestic stock in the park be allowed. Not only would this cause the available food to run out more quickly but it would soon alter the species composition of the range. This could have the most far reaching consequences and rapidly accelerate the degradation of the habitat.

Several methods are available to cut down serious crop raiding by elephants. The most obvious of these, but perhaps the most difficult to implement, is to increase the area of the elephant parks to include land normally used in the dry season. If this is not possible then corridors exclusively for the passage of elephants from wet season to dry season range should be left. Areas of intensive agriculture should be separated from the parks by buffer zones in which some crop raising, on a limited scale and for a limited period of time (so that the vegetation can revert to climax every so often) could be permitted. Some damage must be expected in these zones, but the more productive paddy fields beyond should be protected. If the buffers fail in places, electric fences—which are most effective against elephants if they

are regularly patrolled and maintained—should be erected.

It would be wrong to suggest that Ceylon has either too many or too few elephants, although it is said that King Raja Sinha I in 1588 raised 2,200 elephants locally, and with little effort, for his attack on the Portuguese fort at Colombo. It is unlikely he could do the same today with the same effort. The country has an elephant population in balance with its supporting ecosystem. Today, however, with the need for increased agricultural production never greater, that balance is under threat. There has seldom been such a clear-cut possibility for ecosystem conservation.

MEMBRANES

All Change

from a Correspondent

SEVERAL studies with the scanning electron microscope have recently been made of the surface of normal and transformed cells. Without a doubt, the most beautiful and informative pictures published so far appeared in the May issue of the *Journal of Cell Biology* (57, 815; 1973) in articles by Porter, Prescott and Frye and by Rubin and Everhart. Porter *et al.* followed changes in the surface morphology of a synchronized but dense population of Chinese hamster ovary cells during different phases of the cell cycle, and found that after mitosis, as the cells begin to spread out, there is a high incidence of "blebs" or bubble-like protuberances of the cytoplasm, intermingled with numerous, small microvilli. The photographs also show the most extraordinary long, thin filopodia extending from the cytoplasm to the surface of the coverslip or to neighbouring cells. As the S phase is traversed, and the cells begin to spread out more thinly and to touch one another, the blebs disappear and the number of microvilli is reduced, but as the cells prepare for mitosis again the microvilli reappear and by late G₂ the rounded cells are almost entirely covered by these structures.

Previously it had been shown (Puck *et al.*, *Proc. natn. Acad. Sci., U.S.A.*, **69**, 1943; 1972) that treatment of CHO cells with cyclic AMP and testosterone inhibited the appearance of "violently extending and retracting knob-like structures" on the cell surface and caused the cells to extend into fibroblast-like shape. Treatment of extended cells with cytochalasin B or colcemid (agents which disorganize microfilament or microtubule components respectively) caused the appearance of knobs. It is therefore interesting that Porter *et al.* state that in CHO cells treated with cyclic AMP there is obvious alignment of microtubules parallel with the long axis

of the cell, whereas there is little or no apparent organization in normal CHO cells.

Antagonism between the effects of cyclic AMP and colchicine of another kind is now reported by Kram and Tomkins (*Proc. natn. Acad. Sci., U.S.A.*, **70**, 1659; 1973) who have extended studies on the inhibitory effect of cyclic AMP on the serum-stimulated uptake of low molecular weight metabolites by 3T3 cells. They found that this inhibition is overcome specifically by cyclic GMP, and also by vinblastine and colchicine. Moreover, the last two substances stimulate uridine uptake in serum-deprived cells (without affecting the intracellular level of cyclic AMP), but cytochalasin B had no effect.

It remains to be seen how these biochemical changes in the state of the cell membrane relate to the morphological changes seen with cyclic AMP and other agents affecting microtubule assembly. Returning to the electron microscopy of cell membranes, the same issue of the *Proceedings* contains an article by Gregg and Nesom (*ibid.*, 1630) on the response of amoebae of the slime mould *Dictyostelium* to cyclic AMP. When they used the freeze-fracture technique to look at the inner surface of the plasma membrane, they observed numerous protuberances which averaged 60 Å in diameter. Several hours after exposing the amoebae to cyclic AMP the size of these particles, which probably represent proteins or clusters of proteins em-

bedded in the phospholipid bilayer, had increased about 1.7 times. Again the relationship between these morphological changes and biochemical alterations in the membrane leading to increased adhesiveness of the cells remains to be determined.

HUMAN ADAPTABILITY

Biology of New Guineans

from a Correspondent

A DISCUSSION meeting on human adaptability in a tropical ecosystem at the Royal Society on June 21 brought together most of the participants in a multidisciplinary study which involved investigations, jointly sponsored by the Royal Society of London and the Australian Academy of Sciences, on two contrasting populations in New Guinea; one a coastal group living in hot humid conditions on a small fertile island, Kar Kar, and the other living in a mountainous region near Goroka.

Apart from the intrinsic biological interest of the New Guineans, Professor R. J. Walsh (University of New South Wales) emphasized the short time that remains before the whole traditional pattern of life in New Guinea becomes irrevocably altered by European influence. He also mentioned one of the disturbing effects of a large-scale multidisciplinary investigation on unsophisticated peoples; apparently considerable resentment eventually arose in the

The Third Strand

It has been pointed out that the preferred conformations of mononucleotides are conserved in DNA and RNA double helices. Arnott and Bond in next Wednesday's *Nature new Biology* present further evidence that they are also conserved in the third strand of triple helical complexes of synthetic polynucleotides. They studied, by X-ray diffraction, fibres drawn from the three stranded complex poly(U).poly(A).poly(U). This they show can exist as a 12 or 11-fold triple helix according to the humidity, but replacement of the poly(A) by poly(dA) gives only the 11-fold helix. To a first approximation either structure can be viewed as a standard complex of poly(A).poly(U) with Watson-Crick base pairing between antiparallel strands in a configuration closely resembling A'-RNA and with the third strand of poly(U) coiled up in the major groove and running parallel to the poly(A). The strands are aligned in the fibre in a hexagonal net with screw disorder as in A''-RNA. A striking result is that the conformational angles of all three strands are similar to those found in A-RNA, and that the structure is

remarkably compact with a minimum effective diameter scarcely greater than A-RNA. This structure is isogeometrical to poly(C).poly(G).poly(C)—in the form with one extra proton. It is thus possible that three stranded helices could form in RNA if built round a central strand with a run of purines. Such structures may be of biological significance in the structure of chromosomes or in the role of poly(A) sequences in messenger RNA.

Similar conclusions concerning the conservation of conformation angles were previously drawn by Arnott and Bond (*Science, N.Y.*, **181**, 68; 1973) in their study of poly(I).poly(A).poly(I). This is the more remarkable because only purine bases are involved. In this structure one strand of poly(I) ran antiparallel to the poly(A) and the other parallel. Although the interglycosidic link distance was different from the Watson-Crick value for the antiparallel poly(A).poly(I) interaction—13.0 Å—they suggested that this conformation was the one used in anticodon-codon interactions in the wobble position.

coastal people of Kar Kar by reason of the multitude of tests to which they had been exposed with no apparent direct or indirect benefit to them. They felt exploited for the purposes of the Europeans.

Several speakers dealt with the genetic information. Dr A. E. Mourant (St Bartholomew's Hospital, London) has assembled more data on red cell enzymes in New Guinean people than on any other peoples in the world. Some of the new genetic markers, such as haemoglobin-J, first discovered 6 years ago in the islands of the south-west Pacific (discussed by Dr G. H. Beaven, National Institute for Medical Research, London) have great significance for studying population movements and variability. The movement, relatedness and genetic structure of the coastal New Guinean people of Kar Kar, and the genetic distances between certain adjacent language groups (of the order of 3,000–4,000 years), were discussed by Dr G. A. Harrison (University of Oxford) and Dr P. B. Booth (Christchurch Hospital, New Zealand) respectively.

Some peculiarities of growth and physique were described by Mr R. G. Harvey (University of Surrey). The age of menarche is 18 years or later in some highland girls. There is a decrease in body weight with ageing from young adulthood onwards in both males and females—a remarkable contrast to European and North American people.

In some respects, the most interesting results on the New Guineans were reserved for the afternoon session. Health studies (Dr R. W. Hornabrook, Institute of Human Biology, Papua-New Guinea) have shown an almost complete absence of the diseases of Western society—hypertension, cardiovascular degenerative disease and diabetes mellitus. Dr J. V. G. A. Durnin and Dr N. G. Norgan (University of Glasgow) discussed various aspects of the exceptional nutritional findings. The physique of the New Guineans, especially the men and the young women, is excellent; their way of life entails a good deal of moderately hard work and yet the energy and protein intake in their diet is very low—1,400 and 1,900 kcal/day for the coastal women and men respectively and 2,100 and 2,500 kcal/day for the highland women and men. There is no obesity and the fat content of the men and women is the equivalent of that found in athletes in Europe, and middle aged people are no fatter than young adults.

Dr J. E. Cotes (MRC Pneumoconiosis Unit, Cardiff) and Dr J. M. Patrick (University of Ife, Nigeria) described lung function and exercise capacity, which again are comparable to very athletic people in the United Kingdom. Many of the New Guineans smoke native leaf tobacco, which has appar-

ently no measurable effect on lung function.

Tests on temperature regulation, carried out by Dr R. H. Fox (MRC Human Physiology Division, London) and Dr G. M. Budd (University of Sydney), indicate peculiar and unusual adaptation. Exposure to a standard heat load produced similar deep body and skin temperatures in New Guineans compared with acclimatized Europeans, but much smaller sweat loss—showing an ability to conserve body fluid without restricting heat loss by the evaporation of sweat.

The meeting produced many glimpses into the extraordinarily interesting biology of the remarkable peoples of New Guinea. The new information on genetics, nutrition and physiology has wide-ranging implications.

FISHERIES

Acoustic Methods

from a Correspondent

ACOUSTIC methods in fisheries research was the topic of a symposium organized by the International Council for the Exploration of the Sea with the collaboration of the Food and Agriculture Organization of the United Nations and the International Commission for the Northwest Atlantic Fisheries in Bergen on June 19 to 22. The scope of the meeting included investigations of the seabed, study of fish behaviour and the action of fishing gear, estimation of fish abundance and description of fish stocks; the last of these topics was accorded most attention.

Because fisheries biologists in the past have been unable to see and count directly fish in the sea they have used indirect methods involving tedious sampling and elaborate mathematical models and calculations to make quantitative estimates of stocks. Now acoustic echo techniques have been developed not just to find fish but to quantify the received echoes. Electric counting, integrating and computing systems are being developed in many countries for assessing fish populations by high speed surveys. A striking illustration of the use and potential of the echo-integrating technique, whereby the voltages of the returned signals from fish in a series of water layers are summed, was provided by Mr L. Middtun and Mr O. Nakken (Institute of Marine Research, Bergen); in about two weeks, with one research vessel, they had plotted the distribution of the Barents Sea capelin and estimated the size of the spawning stock to be between 2.0×10^6 and 3.1×10^6 tons, which agrees well with estimates made by the classical indirect methods. They had also similarly mapped blue whiting to the north-west and west of the British Isles and estimated the spawning of stock to be between 4.0×10^6 and

8.0×10^6 tons which indicates a big fishery potential of this unexploited species. Dr R. Thorne (University of Washington) obtained in near ideal conditions of single species in partially enclosed waters an encouraging linear relationship between his acoustic integrator estimates and fishing catches of Pacific hake and herring.

Acoustic echo techniques are also being tried for identifying species of fish and for estimating their sizes; for these methods and for estimating abundance a knowledge of target strengths of fish is essential. Mr J. Suomala (C. S. Draper Laboratory, MIT) presented an analysis of echoes from up to 1,000 floats which simulated various arrays of fish in a water-filled tank of 9.5 m diameter. Mr O. Nakken and Mr K. Olsen (Institute of Marine Research, Bergen) measured target strengths of real but dead fish fixed below the echo-meter in various aspects, and Dr G. Goddard (University of Birmingham) and Mr K. Johannesson (FAO, Rome) had used caged live fish. The variations of target strength with fish aspect are very big—much larger than the differences between species, so that identification of fish by echoes is not likely and acoustic surveys must include sample fishing. In an interesting note Mr S. Olsen (FAO, India) pointed out that, whereas the echo from a fish is usually dependent on its air bladder, the shape of the porcupine fish causes it to act rather like a radar reflector and so it has an anomalous target strength.

Mr W. Acker (University of Washington) overcame the problem of counting salmon in surface waters by submerging echo-meters transmitting upwards. With ingenious use of the Doppler effect to assist in measuring swimming speeds of fish, and to study the internal dynamics of fish shoals, Dr D. Holliday (TRACOR Inc., San Diego) estimated the mean size of fish by using the number of body lengths travelled per second at average cruising and burst speeds, thus neatly illustrating the interdependence of biologists and physicists in this field.

In a section devoted to use of acoustics in fishing gear and fish behaviour research, Dr S. Rusby (now Institute of Oceanographic Sciences, Godalming) showed that the 6.4 kHz GLORIA system developed at the National Institute of Oceanography (now the Institute of Oceanographic Sciences) provided an excellent method of studying the distribution, size, shape and movement of pelagic fish shoals at ranges up to 20 km. Alongside this the ARL sector-scanning sonar is unrivalled for detailed shorter range observation; it had been used by Dr D. Cushing (Fisheries Laboratory, Lowestoft) to observe fish shoal packing densities directly and by a group of colleagues at Lowestoft to observe fish reaction to a trawl and to measure trawl efficiency.

SOLID STATE

Optical Circuits

from a Correspondent

ALMOST everyone has felt the impact of miniaturization in electronic circuits. TVs and radios have become portable and now calculating machines are following. This has been achieved almost entirely by the replacement of the vacuum tube by the transistor and, for the more complex circuits, by the packing of many hundreds or thousands of transistors onto one silicon chip. Nowadays, a computer can be put on a single integrated circuit. The next stage of development in integrated circuitry will almost certainly be the partial change-over to the use of optical signals for transferring data, but again in very small integrated devices. The chief reason is the better speed of operation which can be obtained when information is impressed on a light beam, rather than on a bar of semiconductor. For this reason, we are already witnessing the use of laser links between distant computers (and soon between satellites in space), whereas land lines consisting of bunches of optical fibres could ultimately replace our present telephone cables, endowing vastly greater carrying capacity to the country's communication system. Apart from the speed and flexibility of optical information processing, however, two other major technical needs may be fulfilled by optical methods, namely the need for more compact storage of information and the need for an all-solid-state camera. Thus, "Optoelectronics" is a field of research which should be watched closely by those with interests in wide-band data transmission, information processing and imaging.

One recent step which should be noted is the making of an integrated optical photodetector. This device is capable of having a laser signal piped along its surface for any reasonable distance, then be deflected into a lower layer, where it is converted into an electrical signal. Whereas the concept is clearly not novel, the realization of the concept has been achieved rather neatly and very economically. The light guide is a sputtered glass film, bounded on one surface by air and on the other by thermally grown silicon dioxide, formed by oxidation of a silicon surface, out of which the sensing photodiode is formed. The authors, D. B. Ostrowsky, R. Poirier, L. M. Reiber and C. Deverdun, in *Appl. Phys. Letts.*, **22** (9), 463; 1973, describe the use of the ordinary materials of silicon technology for making such a thin-film light guide having quite a high efficiency. Because the structure of the device is amenable to all the tricks of miniaturization and complex pattern generation by photolithography, very complex in-

formation processing circuitry could be developed rather rapidly in this system of materials. Thus, within a few years of the development of a thin-film light guide by Tien and Ulrich (*J. opt. Soc. Am.*, **60**, 1325; 1970), an easily fabricated, integral optical-electrical circuit element has been demonstrated.

The efficiencies are as follows: losses in the sputtered glass film, which has a refractive index of 1.46 and is 1 μm thick, are 0.8 dB per cm from all sources, of which 0.1 dB per cm is unavoidable leakage loss into the substrate. The guide-diode coupling achieved was 80%. Even using a crude grating, made of photoresist, to couple a laser beam into the thin film, good laser-film coupling was achieved. The rise-time of the diode signal was limited by the capacitance of the diode but could reasonably be reduced to 15×10^{-12} s—a very low value for silicon which is possible because the photodiode can be made very small in this application. This, in turn, being because a very energy-dense optical signal is being transmitted.

Thus, this new device demonstrates some of the basic advantages of using light rather than electrical current as a medium by which to process signals. Optical integrated circuits, coupled to holographic information stores, may in a few years make our present pocket-sized computers look very cumbersome and indeed senile.

Experimental and Theoretical Aerosols

How aerosols are formed is a question which is still causing a great deal of discussion and the flow of publications on the subject is still increasing. In next Monday's *Nature Physical Science* (July 23) two aspects of the science of aerosols are given an airing. First Kiang, Stauffer and Mohnen present a theoretical interpretation of the way in which aerosols are formed. In another communication, which deals with an aspect of the experimental side of aerosol physics, Dahneke summarizes recent developments in aerosol beam spectrometry.

Kiang and colleagues point out that there have been many studies both of the chemical reactions which occur in the liquid phase of droplets and of the role of chemical reactions preceding the phase transitions. But none of these studies has given any consideration to the physical processes which take place in the formation of aerosols. Kiang *et al.* have applied themselves to investigating the nucleation process but they also call attention to the possible chemical reactions involved in the formation of $(\text{NH}_4)_2\text{SO}_4$. They conclude that water vapour plays an important part in heteromolecular nucleation in that it can change the

ASTHENOSPHERE

Three Possible Models

from our Geomagnetism Correspondent

THE general properties of the low velocity zone in the Earth's upper mantle are now quite well known. Depending upon the region, the top of the zone lies between 50 and 100 km beneath the surface and the bottom lies between 100 and 200 km, although in spite of this variability both the upper and lower boundaries appear to be sharp, with each transition taking place in less than 10 km. The velocity drop which gives its name to the zone is about 3–6% and according to Anderson *et al.* (*J. geophys. Res.*, **70**, 1991; 1965) is rather more pronounced for S waves than for P waves. This difference in behaviour can apparently be related partly to the fact that the attenuation is greater for shear waves than for compressional waves and is a useful reminder that the low velocity zone is also a high attenuation zone, the increased attenuation also being a few per cent.

As Gueguen and Mercier (*Phys. Earth planet. Int.*, **7**, 39; 1973) now point out, it follows from this that, although explanations for low velocity and high attenuation have often been considered independently, valid physical or chemical models for the low velocity-high attenuation zone (LVHAZ) must

rate of nucleation by several orders of magnitude. Perhaps it is no surprise that the calculations reveal that gaseous substances with the lowest volatility will nucleate first, but Kiang and his team point out that the critically sized droplets so formed will act as a surface for heteromolecular condensation. The significance of this work is that the theory developed can be used for the formation of aerosols in urban atmospheres, the stratosphere and also in the atmospheres of planets.

The surprising aspect of Dahneke's review of aerosol beam spectrometry is that evaporation does not seem to pose a serious problem in the measurement of moist aerosols. The reason, quite simply, is that the particles are substantially cooled in the adiabatically expanding nozzle-jet flow and this, coupled with evaporative cooling, retards further evaporation. Thus, these spectrometers may prove to be widely useful in measuring aerodynamic size distributions, compound size/composition, size/radioactivity and size/charge distribution of aerosols. They can also be used in sorting the sizes of airborne particles, powdered and industrial powders and dusts.

account for both phenomena. In practice, this is not quite so serious an indictment of previous work as it may appear, for it happens that some of the explanations proposed for one phenomenon automatically take account of the other. This is particularly true for the most favoured explanation for the low velocity—partial melting—which also implies high attenuation. On the other hand, the need for a dual explanation does rule out certain other proposed effects, such as scattering, dislocation damping and thermoelasticity. After rejecting some other (including dual) models on various grounds, Gueguen and Mercier conclude that, of previously proposed explanations, only partial melting or the presence of viscous grain boundaries can adequately explain the two chief features of the LVHAZ.

But they also examine in detail a third possibility — dislocation-impurity interactions—which, though apparently not considered much before, is in their view as likely as the other two. Certainly the presence of dislocations (either inside grains or at grain boundaries) together with impurities can be shown to be related to attenuation. For example, Jackson (*Grain Boundary Relaxation and the Attenuation of Seismic Waves*, thesis, MIT, Cambridge, 1969) demonstrated that, at temperatures near the melting point, a rapid increase in attenuation occurs in polycrystals and in previously deformed single crystals and that this attenuation depends on the nature of the impurities present. Moreover, Chang (*J. appl. Phys.*, **32**, 1127; 1961) observed an impurity-dependent relaxation peak in both single crystals and polycrystals of Al_2O_3 at temperatures of about half the melting point.

Gueguen and Mercier now show formally that the experimental data obtained by Chang and Jackson are consistent with a model in which dislocations interact with point defects. Moreover, they also show that this mechanism can lead to a seismic velocity decrease and an attenuation at least as great as those actually observed.

On the face of it, there is still little reason to discard the idea of partial melting, although by the same token there may be no case for particularly favouring it over the other two explanations. Of course, part of the independent support for partial melting comes from the occurrence of volcanism; but as Gueguen and Mercier point out, there need not necessarily be any connexion between a partially molten LVHAZ and magma appearing at the Earth's surface. Near-surface melting could be produced by, for example, adiabatic decompression of material undergoing upward transport, thereby resulting in fusion. Moreover, partial melting is not the only mechanism

capable of producing a plastic zone susceptible to flow, for dislocations are also known to induce plastic behaviour.

But there is even more to it than that. Ironically, the expression for viscosity obtained by Gueguen and Mercier on the basis of dislocation-impurity theory is formally identical to that obtained by Walsh (*J. geophys. Res.*, **73**, 4333; 1969) in the basis of partial melting theory. The reason for this is apparently that grain boundaries are neither liquid nor solid but an intermediate state, so that Walsh's approach using a viscous (liquid-state) phase between grains and the Gueguen-Mercier approach regarding boundaries as an array of dislocations in a solid are, under certain circumstances, equally valid approximations to the real situation. What this means is that it is not possible to use seismic data alone to distinguish between the partial melting attenuation model and the dislocation-point defect interaction attenuation model.

LOW TEMPERATURE PHYSICS

Ions in Liquid ^3He

from a Correspondent

A NOVEL technique for measuring the mobility of ions in liquid ^3He has been devised by P. V. E. McClintock of the University of Lancaster (*J. low Temp. Phys.*, **11**, 277; 1973), which has important implications for future ion experiments in the mK temperature range.

Like the common isotope ^4He , liquid ^3He displays exotic properties at very low temperatures but, unlike the case of ^4He , these properties do not manifest themselves suddenly on the low temperature side of a phase transition. Rather, there is a gradual change from classical behaviour above 2 K to a regime where the behaviour is completely dominated by quantum statistics below a few tenths of a Kelvin. Because ^3He is a fermion, and therefore subject to the restriction that only a single particle is allowed to occupy one quantum state, whereas ^4He is a boson, for which multiple occupancy is permitted, the low temperature properties of the two liquids are completely different.

One way in which liquid ^3He differs from ^4He is that, far from becoming superfluid (except, perhaps, under high pressure near 2 mK), its viscosity actually increases with falling temperature. This can be understood in that nearly all the low-lying energy states will be occupied, up to some maximum energy ϵ_F , known as the Fermi energy, near which lie the only accessible empty states. Thus, the only atoms whose states can easily be changed will be those with energies close to ϵ_F . Because, as the temperature is reduced, there are progressively fewer states into which they can be scattered, the difficulty encoun-

tered in changing the liquid's macroscopic configuration, that is, the viscosity, will increase, in agreement with experiment.

Much information on the nature of both the liquid isotopes has been gained from studying the motion of ions, and one quantity which is of interest is the mobility μ , that is the ion's equilibrium drift velocity divided by the electric field causing it to move. In the case of ^3He , the progressive depletion with falling temperature of the number of empty states near ϵ_F into which an atom can be scattered means the probability that an ion will be able to interact with any particular atom which it encounters is going to decrease, so that μ should increase with falling temperature.

The theoretical conclusion, therefore, is that the viscosity and charge mobility should both increase with falling temperature, that is the "thicker" the liquid becomes the more easily the ions should slip through it.

Early attempts to measure mobilities in ^3He ran into difficulties arising partly from the type of ion source which was used. A. C. Anderson, M. Kuchnir and J. C. Wheatley, then of the University of Illinois (*Phys. Rev.*, **168**, 261; 1968), used a radioactive source to generate the ions, and the thermal gradient set up in the liquid by radioactive heating at this source seems to have been, in part, responsible for a very large scatter in their measurements. It did appear, however, that the positive ion mobility was indeed increasing with falling temperature, although much more slowly than had been predicted.

A novel feature of the technique developed by McClintock lies in the use of a field-emission ionization ion source consisting, basically, of an exceedingly sharp tungsten point which, raised to a potential of a few kilovolts, is able to inject ions of either sign into the liquid. The great merit of this source is that it can be pulsed, and so generates heat only when it is actually running, unlike radioactive sources which heat the liquid continuously. The measurements show very much less scatter than those of the Illinois group, and have enabled a hitherto unsuspected minimum in μ , possibly representing the transition from classical to quantum behaviour, to be resolved.

It is particularly desirable that the experiments be extended to the region below 10 mK, for which some rather bizarre behaviour has been predicted by R. M. Bowley of Nottingham University (*J. Phys.*, **C4**, L207; 1970). He believes that there is a regime in which, for any given electric field, the mobility will be treble-valued, that is an ion will have three, equally valid, equilibrium drift velocities to choose from. Experiments based on this source should enable this prediction to be tested.

Discovery and Naming of the Isotopes of Element 91

KASIMIR FAJANS

Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48104

DONALD F. C. MORRIS

Nuclear Science Centre, School of Chemistry, Brunel University, Uxbridge UB8 3PH

The history of the discovery and naming of the three naturally occurring isotopes of element 91 is outlined in order to eliminate contradictions to be found in the literature. Information about the nineteen isotopes of protactinium now known is listed.

THERE are several discrepancies in the literature concerning the discovery of element 91. For example, the statement in a recent obituary¹ of John Arnold Cranston . . . "In the course of his work he had discovered a new terrestrial element, protoactinium—element 91" . . . is misleading.

At the time of the placing of the radioelements in the periodic system it was predicted^{2,3} that uranium X might be a mixture of two consecutive radioelements uranium X₁ and uranium X₂. This followed from the then newly established displacement laws, according to which the beginning of the uranium series should be formulated as



Periodic Group VI IV V VI IV

This is now known to correspond to



but no radioelement was known at that time in Group V at the place in the Periodic Table between thorium and uranium.

In attempting to find uranium X₂, Fajans and Göhring⁴ applied the generalization⁵ that after a beta transformation the daughter element is electrochemically more noble than the mother element. A solution of uranium X was placed in a lead dish, with the expectation that "ekatantalum" is more, thorium less, noble than lead. In fact, radioactive material was formed on the surface of the lead dish and its β⁻ activity decayed with the previously not known half life, 1.1 min. Its chemical nature was further confirmed⁵ by its coprecipitation from solution with hydrous tantalum(V) oxide.

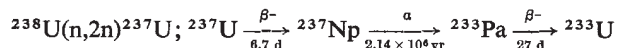
Because uranium X₂ occupied a previously vacant space in the periodic system (it constituted a new element), the nuclide received⁶ the distinctive name brevium (Bv), suggested by its short life.

The discovery of the next isotope of element 91 was due to the search for the immediate precursor of actinium, which according to the displacement laws could be formed by an unknown radionuclide ? (Group V) $\xrightarrow{\alpha}$ Ac (Group III). Indeed, Soddy and Cranston⁷, and independently Hahn and Meitner⁸, separated from uranium minerals fractions having the chemical behaviour of brevium in which they found the production of actinium. The half life of the new radionuclide was initially estimated⁸ to be between 1.2×10^3 and 1.8×10^5 yr; it is now known to be 3.27×10^4 yr. Hahn and Meitner named it protactinium (²³¹Pa) because it was the progenitor of actinium. This isotope is much more stable than UX₂, so Fajans⁹ proposed that the name of element 91 be changed from brevium

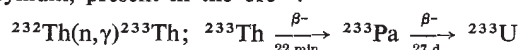
to protactinium. This corresponded to the then common usage that the element's name was that of its longest lived isotope.

The third isotope of element 91 was discovered by Hahn¹⁰ who found that UX₁ produces not only UX₂ but, to an extent shown later to be only 0.13%, also UZ of a half life of 6.7 h. It is not merely isotopic with UX₂ but has the same mass number 234 and the pair is considered as the first example of nuclear isomerism.

The three isotopes of protactinium ²³¹Pa, ²³⁴Pa^m(UX₂) and ²³⁴Pa(UZ) are those found in nature. ²³¹Pa is a member of the actinouranium (4n+3) radioactive series and the pair of isomers belongs to the uranium–radium (4n+2) series. Even the richest ores of uranium contain only about 1 part of Pa in 10⁷. Nevertheless, in 1962 it was reported that well over 100 g of protactinium had been isolated by the United Kingdom Atomic Energy Authority from some 60 t of accumulated sludges from a uranium extraction process¹³. To be strictly accurate ²³³Pa, a member of the (4n+1) series, does occur in nature, but only to a tiny extent. It has been established¹¹ that minute amounts of ²³⁷Np and ²³³U are continuously produced in uranium ores by nuclear reactions brought about by neutrons resulting from spontaneous fission of uranium.



In thorium ores ²³³Pa may be produced by reactions initiated by neutrons arising from the action of energetic α particles from the heavy elements on the nuclei of light elements, such as beryllium, present in the ore¹².



In addition to the radioisotopes of protactinium occurring in uranium minerals, many others have been prepared artificially. The lightest has mass number 216, the heaviest 238. First to be produced¹⁴ was ²³³Pa in 1938; the others were discovered from 1948 onwards. A list of the isotopes known now is given in Table 1. The half lives of the artificially produced radionuclides range between 5.7 ms (²²²Pa) and 27 d (²³³Pa). The latter is nearly 5×10^8 times longer than the former and nearly 5×10^5 times shorter than the half life of ²³¹Pa. Several isotopes of protactinium are constituents of well characterized collateral series^{12,16,19–22}.

The data for the isotopes listed in Table 1 correspond, with a few exceptions, to the following three rules found by Fajans³⁰ in 1913: (1) In a pleiad (the term isotope had not yet been used) which contains pure α and pure β emitters the former have a smaller mass than the latter. (2) For α emitters the half life increases with increasing mass. (3) For β emitters the half life decreases with increasing mass. Some more information about the application of these three rules can be found in the report K71–17 (1971) of a lecture at the Third International Protactinium Conference, 1969.

Pronounced exceptions to rule (2) had already been noticed in 1913, and these have proved of importance in the development of the modern theory of nuclear structure and radioactivity. In this context the nuclear characteristics of the lighter isotopes of protactinium merit brief discussion. For a smooth trough-like mass-energy surface a trend of increasing α disintegration energy with decreasing mass number is anticipated³¹ and rule (2) may be expected to be obeyed. But

Table 1 Isotopes of Protactinium

Isotope	Half life	Type of decay, radiations and energies (MeV)	Year and place of discovery	Source	Reference
^{216}Pa	0.2 s	α 7.72, 7.82, 7.92	1971 Dubna	$^{189}\text{Os}(^{31}\text{P}, 4n)$, $^{190}\text{Os}(^{31}\text{P}, 5n)$, $^{197}\text{Au}(^{24}\text{Mg}, 5n)$	15
^{222}Pa	5.7 ms	α 8.16+8.18+8.21, 8.33, 8.54	1968 Berkeley	$^{209}\text{Bi}(^{16}\text{O}, 3n)$, $^{208}\text{Pb}(^{19}\text{F}, 3n)$	16
^{223}Pa	6.5 ms	α 8.01, 8.20	1968 Berkeley	$^{208}\text{Pb}(^{19}\text{F}, 4n)$, $^{205}\text{Tl}(^{22}\text{Ne}, 4n)$, $^{209}\text{Bi}(^{20}\text{Ne}, \alpha 2n)$	16
^{224}Pa	0.95 s	α 7.49	1958 Uppsala	$^{232}\text{Th}(p, 9n)$	17
^{225}Pa	1.8 s	α 7.20, 7.25	1951 Montreal	$^{232}\text{Th}(d, 9n)$	18
^{226}Pa	1.8 min	α 6.86, 6.82; EC	1949 Berkeley	$^{232}\text{Th}(d, 8n)$	19, 21
^{227}Pa	38.3 min	α 6.47, 6.42, 6.40, 6.36; EC; γ	1948 Berkeley	$^{232}\text{Th}(d, 7n)$	20, 19, 21
^{228}Pa	22 h	EC (α 6.11, others); γ	1948 Berkeley	$^{232}\text{Th}(d, 6n)$	20, 21
^{229}Pa	1.5 d	EC (α 5.67–5.32)	1949 Berkeley	$^{230}\text{Th}(d, 3n)$	23
^{230}Pa	17 d	EC; β^- 0.41 max; γ	1948 Chicago	$^{232}\text{Th}(p, 3n)$	24
^{231}Pa	3.27×10^4 yr	α 5.02, 5.01, 4.95 (others); γ	1917 Aberdeen; Berlin–Dahlem	Natural source	7, 8
^{232}Pa	1.31 d	β^- 0.32, 1.34 max; γ	1949 Berkeley	$^{232}\text{Th}(d, 2n)$	25
^{233}Pa	27 d	β^- 0.26, 0.15, 0.57; γ	1938 Berlin–Dahlem	$^{232}\text{Th}(n, \gamma)$, $^{233}\text{Th}(\beta^-)$	14
$^{234}\text{Pa}^m(\text{UX}_2)$	1.17 min	β^- 2.29 (others); (IT; γ)	1913 Karlsruhe	Natural source	4, 5
$^{234}\text{Pa}(\text{UZ})$	6.7 h	β^- 0.50, 0.19 (others); γ	1921 Berlin–Dahlem	Natural source	10
^{235}Pa	24 min	β^- 1.4 max	1950 Chalk River	$^{234}\text{Th}(n, \gamma)$, $^{235}\text{Th}(\beta^-)$	26
^{236}Pa	9.1 min	β^- 3.2 max; γ	1963 Amsterdam	$^{238}\text{U}(d, \alpha)$	27 *
^{237}Pa	8.7 min	β^- 2.3 max; γ	1954 Berkeley	$^{238}\text{U}(d, n2p)$	28 *
^{238}Pa	2.3 min	β^- 2.9 max; γ	1968 Mainz	$^{238}\text{U}(n, p)$	29

* Wolzak and Morinaga²⁷, who are credited with the discovery of protactinium-236, pointed out that the same activity had been observed earlier by Crane and Iddings²⁸ who had assigned it to ^{237}Pa . Protactinium-237 may be prepared²⁹ by the nuclear reactions $^{238}\text{U}(n, pn)$ and $^{238}\text{U}(\gamma, p)$. EC, Electron capture; IT, isomeric transition.

amongst heavy elements a discontinuity in atomic masses occurs at the closed nucleon configuration occurring with a neutron number of 126, and this causes a related discontinuity in the α decay energies¹². Therefore isotopes of protactinium with 126 or fewer neutrons are expected to have lower α disintegration energies and enhanced α partial half lives (Fig. 1). The only isotope in that region for which definite experimental evidence is available is ^{216}Pa , discovered in 1971 by Sung-Chin-Yang *et al.*¹⁵ in osmium targets bombarded with 200 MeV $^{31}\text{P}^{5+}$ ions and in gold targets bombarded with

146 MeV ^{24}Mg ions, and which has a half life of 0.2 s. This represents a striking increase in stability over that of the protactinium isotopes of mass numbers 222 and 223.

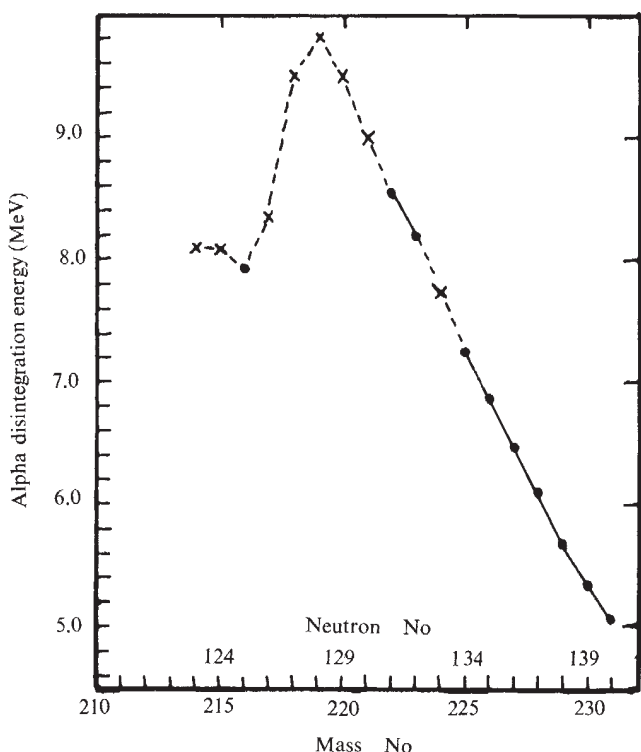


Fig. 1 Alpha particle energy (for ground-state transition) as a function of mass number of protactinium isotopes. ●, Experimental data; ×, predictions^{16,32}.

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Coherence in Transpacific Movements of Positive and Negative Anomalies of Sea Surface Temperature, 1953-60

FELIX FAVORITE

Northwest Fisheries Center, National Marine Fisheries Service, National Oceanic and Atmospheric Administration, 2725 Montlake Boulevard East, Seattle, Washington 98112

DOUGLAS R. McLAIN

Pacific Environmental Group, National Marine Fisheries Service, National Oceanic and Atmospheric Administration, c/o Fleet Numerical Weather Central, Monterey, California 93940

Computer analyses of 2 million observations of sea surface temperature provide evidence of orderly transpacific movements of large areas of anomalous warm and cold-surface water which greatly influence environmental conditions off the west coasts of the United States and Canada. These quasipermanent features seem to move around the North Pacific gyre, roughly 180° out of phase, with periods of 5-6 yr.

INVESTIGATION of the relations between the oceanic distributions of fishes, such as the Pacific salmon, and their environment requires the piecing together of fragmentary information collected by independent research vessels. We have been charged by the American Section of the International North Pacific Fisheries Commission with responsibility for summarizing environmental investigations in the central part of the Subarctic Pacific region (generally defined as transpacific north of 40° N) for 1960-72. We have also used surface observations by ships of opportunity between 35 and 50° N because of the paucity of oceanographic stations in that area.

The observations were assembled by the National Climatic Center (Tape Data Family-11) and were programmed for computer analyses by the Fleet Numerical Weather Central and the Pacific Environmental Group of the National Marine Fisheries Service. Data before 1940 are quite complete for several decades in some coastal areas off Japan and the west coast of the United States but are sparse in oceanic areas; data for the wartime period 1940-47 are limited. Monthly data for 1948-67 are reasonably complete in 5° by 5° quadrangles, and anomalies used in this report are based on monthly and annual mean values for this 20 year period (sixty-two of the seventy-two quadrangles had sequential monthly data for 18 or more years).

In seeking continuity of these data in time and space, we have uncovered new information concerning the anomalous conditions during the latter half of the 1950s and on the general periodicity of such phenomenon which is of sufficient interest to report at this time because it will markedly affect

past interpretations, present understanding and future investigations not only of oceanographic conditions but of biological and meteorological conditions and interactions as well.

Unusual Conditions, 1957-58

Widespread unusual environmental conditions were reported along the west coast of North America in 1957 and 1958. In the summer of 1957, the highest sea surface temperatures in 21 years occurred at La Jolla, California, and the ice limit at Point Barrow, Alaska, reportedly receded northwards at the earliest recorded period. Extreme positive anomalies of sea surface temperature and accompanying increases in sea level at La Jolla, California, occurred during November 1957 to February 1958. As reports of anomalous warm conditions and record northward sightings and catches of marine life along the coast continued to increase, an unprecedented and impromptu symposium attended by US marine scientists from the Atlantic and Pacific coasts was held at Rancho Sante Fe, California, in June 1958 (ref. 1).

Anomalous conditions had occurred as early as spring 1956 when sea surface temperatures at Christmas Island (1° 59' N, 157° 29' W) indicated anomalous warming, which continued through 1958. Evidence of unusual conditions was also obtained early in 1957 when Canton Island (2° 48' S, 171° 43' W) received an abnormally heavy rainfall, the first in 4 years. Available information, ranging from drift bottle recoveries to sunspot data, presented at the symposium was admittedly fragmentary, largely descriptive, and in some cases confusing, but it was concluded that, even though small perturbations were common occurrences throughout the Pacific Ocean, the events in 1956 were only premonitory and without a clearly discernible connexion with subsequent developments which terminated a remarkable and unprecedented, monotonous decade in regard to the ocean environment. This does not, however, seem to have been the case.

An attempt to find the cause of these developments by comparing meteorological conditions at sea level and 700 mbar in the northern hemisphere and sea surface temperature anomalies in the eastern North Pacific Ocean during 1957-68 was initiated by Namias². No order was found in the "chaotic islands of anomalous warmth or cold" at the sea surface except for macroscale features embracing large portions of the ocean. Somewhat variable sea surface conditions were reported north of 40° N from the autumn of

1957 to the winter of 1957–58 and an interplay (involving feedback) between ocean and atmosphere, modified by gradual climatological changes, was suggested as the cause of the warm conditions.

Pronounced northward intrusions of warm water into the Subarctic region—at 145° E in 1955, 160° E in 1956–57, 180° E in 1957, and 125° W in 1958—deduced from circulation patterns, and based on very limited data, were also suggested as a possible cause of the warm conditions³. The extent of these intrusions was believed to be dependent upon interactions between a “quasi-stationary wave” and the intensity of existing flows. A subsequent extensive analysis of monthly mean sea surface temperature anomalies for 1949–62 (ref. 4) indicated several instances of a transpacific quasi-stationary behaviour, and recurring positive and negative anomalies between 30° N and 50° N were attributed to the existence of a standing wave. Another study showed that coherence between monthly mean sea surface temperature patterns in this area was far greater than any known meteorological coherence, and data at 5° grid points indicated that pattern coherence existed for as long as 2 years⁵.

It has been suggested⁶ that there is a servomechanism in the ocean/atmosphere system of the mid-latitude North Pacific Ocean involving a coupling of atmospheric relative vorticity, Sverdrup transport, and the Laplacian of heat flux at the Subarctic frontal zone near $35\text{--}40^\circ$ N at the western side of the ocean. Discussion of this theory is beyond the scope of this article except to note that the servomechanism is supposed to have triggered in winter 1955–56 the anomalous temperature conditions that existed in 1956–58. We will show that a positive anomaly has been established long before this time, but it is possible that some aspects of the servomechanism contributed to an enhancement of the warm conditions.

Patterns of Anomalies, 1953–60

Sea surface temperature in the Subarctic Pacific region is a capricious water property, constantly changing. Having a range of about 10° C from winter to summer, it is quickly altered throughout spring when periods of clear, calm weather, which allow formation of a warm surface layer up to several metres thick, are followed by cloudy, stormy days and subsequent destruction of the layer. By summer, progressive heating, mixing, and diffusion establish a warm, isothermal surface layer extending to 30 m and heat slowly penetrates into the sharp thermocline, which extends from 30 to 100 m. Throughout autumn, surface cooling and mixing induce convective overturn, eroding the entire seasonal surface layer, and by winter isothermal conditions occur to depths greater than 100 m. In addition to disruptive seasonal processes, continuity of anomalous patches of warm or cold water in time and space is also difficult to ascertain from sporadic observations not only because of the turbulent confluence of the cold Oyashio and warm Kuroshio currents off the coast of Japan, where temperature changes at the sea surface of 5° C over a distance of 50 km are not uncommon, but also because of the large areas of divergence and convergence associated with the western Subarctic and Gulf of Alaska gyres located south of the island arc defined by the Alaskan Peninsula, Aleutian Islands, Commander Islands and Kamchatka Peninsula. Thus, it is understandable that charts of sea surface temperature obtained every 10 d or every month, constructed from individual observations, may reflect some disordered variability. When extensive data (approximately 2 million observations) are averaged by individual years in 5° by 5° quadrangles, however, analyses of maxima, minima, and anomalies reveal interesting patterns.

Analyses of mean annual values of sea surface temperature between 1953 and 1960 indicate an orderly west to east displacement of the maxima of the temperature for this

period, commencing off Japan in 1955 and reaching the west coast of North America, from California to Alaska, in 1957 (Fig. 1). The pattern is quite distinct, there being no inconsistent quadrangles except for two between $35\text{--}40^\circ$ N, $150\text{--}165^\circ$ W, and one off the Oregon-California coast in 1959. This apparent transpacific movement corresponds to the generally accepted pattern of geostrophic flow^{7–9}, and generally advanced at a speed of about 5 km d^{-1} slightly less than indicated by geostrophic calculations.

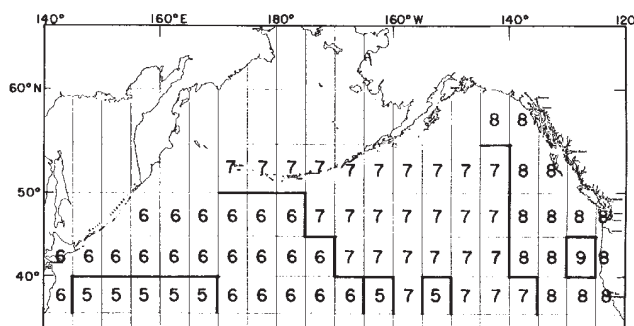


Fig. 1 Distribution of maxima of annual mean sea surface temperature by 5° Marsden quadrants for 1953–60 (number indicates last digit in year maxima occurred).

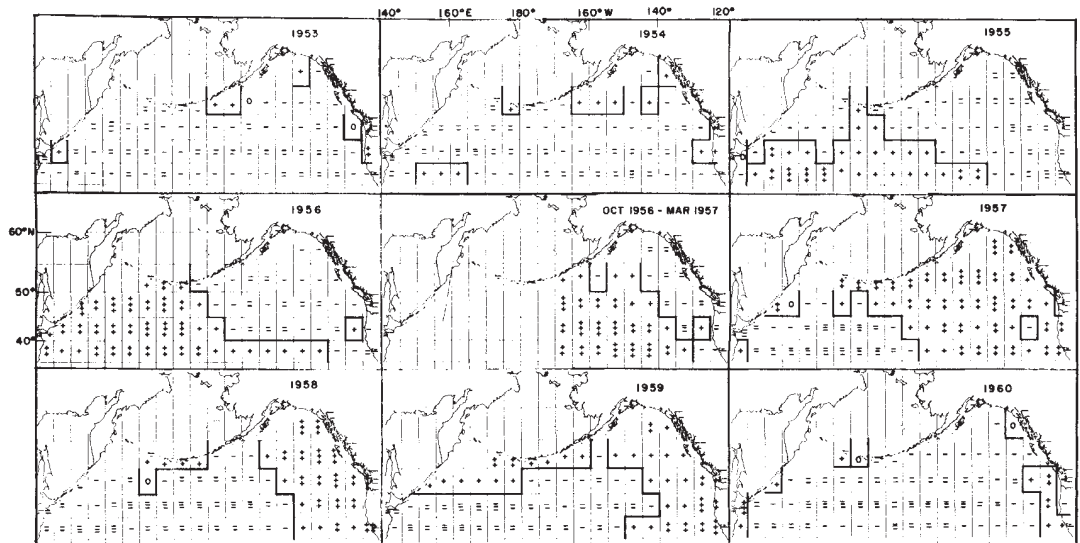
This phenomenon is more detailed in maps of mean annual sea surface temperature anomalies, based upon individual monthly means (Fig. 2). Transpacific negative anomalies occurred north of 35° N in 1953, with the exception of several quadrangles in the Gulf of Alaska and off the west coast of the United States. The coherent eastward advance of the area of positive anomaly across the ocean from 1954 to 1960 is immediately obvious. Positive anomalies occurred in quadrangles off the coast of Japan in 1954 and these increased in number and intensity in 1955; by 1956, quadrangles with positive anomalies in excess of 1° C occurred throughout most of the western part of the ocean. There was a near reversal of transpacific conditions in 1957 and, by 1958, positive anomalies of more than 1° C were found in quadrangles off the west coast of North America. This area of positive anomaly was reduced in 1959, and by 1960 transpacific negative anomalies were again established.

Except for the widespread warming spreading zonally into the eastern Pacific between 35° and 40° N in 1955, and the rather abrupt advance of the area of positive anomaly from the western side to the eastern side of the ocean from 1956 to 1957, the apparent transpacific advance of the area of positive anomaly is convincing. With regard to the former, this location encompasses the Subarctic-Subtropical boundary⁹, and eastward velocities at the south side of this boundary may be higher than presently believed. In addition, analysis of the temperature data on a monthly basis reveals that local short-term surface warming ($+1.5^\circ$ C) occurred near 35° N, 150° W during October, November, and December 1955 and this resulted in mean annual values in this area in 1955 exceeding those of 1956. With regard to the change in conditions between 1956 and 1957, widespread cooling in the central part of the ocean north of 45° N in spring and summer prevented positive anomalies occurring east of 170° W in this area in 1956. The mid-Gulf of Alaska position of the boundary between quadrangles with positive and negative anomalies in autumn and winter 1956–57 (see Fig. 2), however, is convincing evidence of a progressive eastward movement of the warm area. Thus, although influenced by external conditions, the warm area had advanced across the ocean and arrived off the west coast of North America sometime in spring or summer 1957, 3 years later.

Perhaps equally if not more interesting and puzzling is the origin and character of the area of negative anomaly evident downstream and in the wake of the area of positive anomaly. Mean annual temperature minima for 1953–60 occurred in quadrangles at the western side of the ocean in 1953. Extensive cooling in 1953 and 1956 in the central part of the ocean north of 45° N notwithstanding, there was a sufficient number of quadrangles with minima in this area in 1954 to show coherence between minima at the western side of the ocean in 1953 and widespread minima at the eastern side in 1955, which extended one to four quadrangles off the coast, from

at a specific geographic location from one time period to another. This can be done, however, with some confidence in the broader, more diffuse boundary current at the eastern side of the ocean. Anomalous heat content in a water column is evident in temperature data obtained at approximately the same location and time in 1955 and 1958 (Table 1). Although the temperature structure is not typical of that of the general oceanic Subarctic region, the increase in heat content of the water in 1958 is readily apparent; it extended below 100 m and amounted to over $37,000$ calorie cm^{-2} . Maximum temperature difference occurred at about 30 m.

Fig. 2 Distribution of anomalies of annual mean sea surface temperature from 20 yr means (1948–67) by 5° Marsden quadrants (each symbol indicates a 0.5° C increment, that is, ++ signifies a positive anomaly greater than 0.5° C and less than 1.0° C).



California to the northern Gulf of Alaska. This implies a 2–3-year time period for the transpacific advance of this area of negative anomaly.

Periodicity of Anomalies, 1948–67

Transpacific movement of pulses of warm and cold water is apparently a rather common occurrence. Semiannual data from the quadrangle in the central part of the Subarctic region having the largest positive anomaly in 1956 (Marsden square 163, quadrant 1; $40\text{--}45^\circ$ N, $170\text{--}175^\circ$ E) indicate distinctive positive anomalies in this area in 1948 (data incomplete, 1950–51, 1955–56, 1961–62, and 1968, that is, approximately 6-year intervals (Fig. 3)). These positive anomalies last for 1–2 years and are usually immediately preceded by a maximum negative anomaly.

The origin of these pulses is obscure. Further analyses of data south of 35° N revealed positive anomalies of about 0.5° C as early as 1953 in quadrangles at the western side of the ocean between 20 and 30° N, where the annual range of temperature is only about 3° C. The fact that positive anomalies of 1.5° C subsequently existed north of 35° N in 1954, 1955, and 1956 does not necessarily require during these years a marked reduction of heat loss in winter from the sea surface. A northward movement of a surface layer having an abnormally high heat content and its subsequent modification of the environment while subject to slow erosion of its heat content by interactions of the air and sea could produce the same effect. Because of the paucity of data, the turbulent western boundary current, and large-scale interactions at the confluence of the Oyashio and Kuroshio currents, it is difficult to establish normal conditions at any one time or place that would allow the detection of anomalous conditions in a water column at the western side of the ocean, nor is it realistic to compare conditions

An indication of air–sea exchanges in all quadrangles was ascertained for 1948–67 by established computer methods¹⁰. Monthly amounts of incoming, back and reflected radiation, evaporation, and conduction of sensible heat at the sea surface were computed; the resulting semiannual mean energy exchanges, for the same quadrangle in which temperature anomaly data are shown in Fig. 3, are presented in Table 2. Mean energy exchange for the period October to March was -199 calories $\text{cm}^{-2} \text{d}^{-1}$, indicating the large heat loss in this area during autumn and winter months. Anoma-

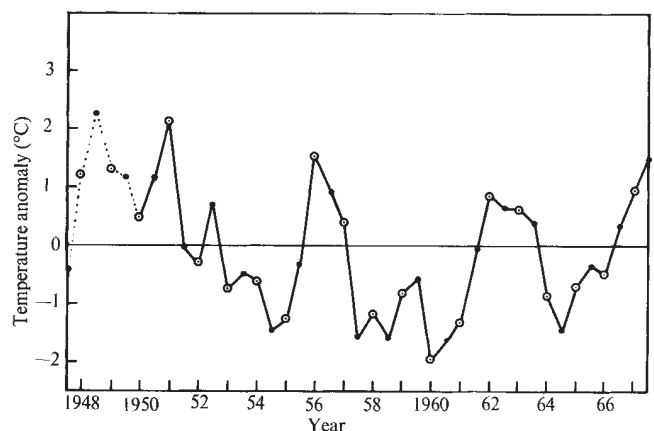


Fig. 3 Semiannual (●, April–September; ○, October–March) anomalies of mean sea surface temperature in Marsden square 163, quadrant 1 ($40\text{--}45^\circ$ N, $170\text{--}175^\circ$ E) from 20 yr mean, 1948–67 (broken line indicates periods for which data are not available for all 6 months).

Table 1 Comparison of Temperature Structure at Approximately the Same Location and Same Time in 1955 and 1958, Indicating Marked Warming in 1958

Date	August 1, 1955	August 2, 1958	
Location	54° 17' N 136° 37' W	55° 00.5' N 136° 00' W	
Vessel	Ste. Therese	Oshawa	
Depth (m)	Temperature (°C)	Temperature (°C)	Difference (°C)
0	12.4	15.6	3.2
10	12.13	15.52	3.39
20	10.30	15.40	5.10
30	8.03	14.95	6.92
50	7.21	10.45	3.24
75	6.40	8.52	2.12
100	6.08	7.09	1.01
150	6.27	6.46	0.19

lously large heat losses occurred from the autumn of 1950 to the winter of 1954. These apparently had little effect on the maximum temperature anomaly in the 1950–51 winter, but losses from 1951–54 correspond to negative temperature anomalies for this period. Anomalously small heat losses from the autumn of 1954 to the winter of 1964 suggest an influence on the maximum positive temperature anomalies that occurred in 1956 and 1962 but little association with the warm pulse in 1967. Similar calculations for other quadrangles in the western side of the ocean show no direct relation to the phenomena discussed here. It should be pointed out, however, that such calculations are largely dependent upon accurate data on cloud thickness and number of cloud layers which are not usually ascertainable by eye from ship-board.

Table 2 Semiannual Anomalies of Sea Surface Temperature (°C) and Total Energy Exchange (calorie cm⁻² d⁻¹) at the Sea Surface in Marsden Square 163, Quadrant 1, Referred to 1948–67 Mean

Year	October–March		Year	April–September	
	Sea surface temperature	Heat exchange*		Sea surface temperature	Heat exchange†
1947–48	1.20	–47 ‡	1948	2.28	79 ‡
1948–49	1.31	31	1949	1.16	60
1949–50	0.43	50	1950	1.21	–7
1950–51	2.14	–83	1951	0.01	–15
1951–52	–0.29	–130	1952	0.71	–12
1952–53	–0.73	–72	1953	–0.45	–15
1953–54	–0.62	–65	1954	–1.45	–40
1954–55	–1.27	55	1955	–0.33	25
1955–56	1.63	5	1956	0.95	42
1956–57	0.41	7	1957	–1.60	7
1957–58	–1.13	26	1958	–1.61	39
1958–59	–0.79	65	1959	–0.54	22
1959–60	–1.91	77	1960	–1.62	14
1960–61	–1.28	24	1961	0.01	21
1961–62	0.82	30	1962	0.68	–33
1962–63	0.66	20	1963	0.42	–18
1963–64	–0.79	37	1964	–1.48	–1
1964–65	–0.66	–13	1965	–0.33	–16
1965–66	–0.44	94	1966	0.39	–30
1966–67	0.98	–103	1967	1.58	–38
1967–68	1.04	–30			

* Mean value –213.

† Mean value 73.

‡ Incomplete data.

We also investigated the possibility of the abrupt transition from maximum negative anomalies to maximum positive anomalies being related to abrupt changes in the intensity of rainfall in equatorial areas. Heavy rainfall usually occurs when the ocean is warmer than the air, and relatively dry periods occur under opposite conditions. Tabulations of extended periods of abnormally heavy and low rainfall in the central and western equatorial Pacific Ocean¹¹ for 1950–60

generally indicate: heavy rainfall during the spring and summer of 1951, throughout 1953, from the spring of 1957 to the summer of 1958, and during the winter of 1958–59; low rainfall occurred from the summer of 1949 to the winter of 1950–51 and from the winter of 1953–54 to the winter of 1956–57. Of these, the latter lasted longest, 3 years, and suggests cold ocean conditions in this area for 1954–56. Although the recently accepted presence of eastward counter-currents¹² in the western North Pacific Ocean near 25° N complicates determination of the time required for this water to appear in the Subarctic region, 2–3 years is a reasonable estimate, and one is tempted to infer a relation between the extended dry period in the equatorial region to the negative anomaly in the Subarctic region during 1957–61. But there are as many contradictions as apparent associations between such phenomena, which is understandable in view of the presence of the equatorial countercurrent, and more study is required.

Bjerknes¹³, after studying positive anomalies of sea surface temperature at Canton Island in 1957–58 (and other years), reported that those conditions occurred in the eastern and central equatorial Pacific Ocean as a result of anomalous weakening of the trade winds of the southern hemisphere and concurrent reduction of equatorial upwelling. It was the sea surface temperature maxima at Canton Island in 1957–58 that implied that the anomalous warming off the west coast of North America might be oceanwide and that possibly reduced circulation in the anticyclonic North Pacific gyre and subsequent peripheral spreading of warm water, previously dynamically held in the central part of the gyre, was the cause of the anomalous conditions. It seems, however, that the anomalous warmings in the Subarctic region near Canton Island in the late 1950s were not directly related.

Relation to North Pacific Gyre

The coherence evident in the Subarctic region during 1953–60 is not as readily apparent during 1948–52 or 1961–67. Cyclic sea surface temperature anomalies with the periodicity presented here, however, have been reported in the western Subarctic region during 1930–41 (ref. 3). Maximum positive anomalies occurred in 1930 and 1937, and maximum negative anomalies in 1934 and 1941. Although relations were suggested between these occurrences and conditions in the eastern Subarctic region, positive anomalies in 1930, 1934, and 1936–41 in this area prevented any convincing argument; it is entirely possible, however, that the lack of correlation was due to the lack of observations during this period. These data would, nevertheless, imply the occurrence of positive anomalies in about 1944 and subsequent continuity with the pulses shown in Fig. 3.

A general estimate, based on geostrophic flow, of the time required for a water parcel to complete one circuit around the North Pacific gyre is 6 years. In view of the evidence presented here, it appears that actually these pulses, although subject to various external and internal influences particularly at the polar front in the western Subarctic region, have the characteristics of a progressive wave having a period of 5–6 years. This would result, at any one location, in reversals of temperature maxima and minima approximately every 3 years and cause conditions off the coasts of Japan and the United States to be 180° out of phase with this approximate periodicity. Preferably one should use semi-annual data when making such comparisons. Caution should be exercised if data from shore stations are used because interactions between the Kuroshio and Oyashio currents can cause simultaneous anomalies of opposite sign for the north-east coast and the south coast of Japan; and seasonal upwelling and shifts in the latitudes of zonal flows and subsequent coastal interactions complicate conditions at the eastern side of the ocean.

If this conclusion is correct, we would expect cold conditions in the eastern Subarctic region (off the west coast of the United States and Canada) in 1970–71 and warm conditions in 1973–74. The former condition has occurred¹⁴, and time will tell about the latter. The forces that could establish this phenomenon, and perhaps sustain it, are not clear at this time. One obvious cause would be 1–3 years of unusually severe winters in the northern half of the gyre and simultaneous unusually warm summers in the southern half. Such events are not evident in available records of sea surface temperatures at coastal stations and, thus, it is not possible at this time to estimate how long the present conditions have existed.

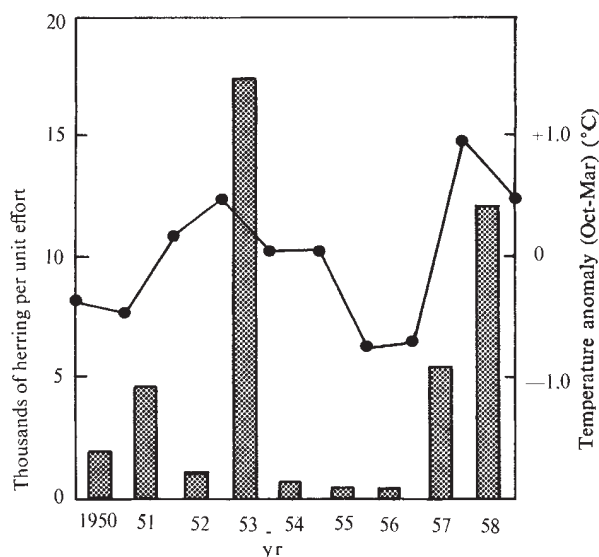


Fig. 4 Comparison of relative abundance of year classes for herring from south-eastern Alaska commercial fishery and anomalies of mean sea surface temperature (October–March) in Marsden square 157, quadrant 1 (referred to 1948–67 mean). ●, Temperature data.

Studies of North Pacific Gyre

There is increasing evidence that in the future, when adequate oceanographic data are obtained, even oceanographers will be surprised at the continuity of oceanic conditions. A good example is the recent evidence that eddies breaking off from the Gulf Stream have maintained their integrity for several months and sometimes for up to a year. Although not able at this time to ascertain the cause for the phenomenon, we have presented evidence that areas of positive and negative anomalies of sea surface temperature in the North Pacific gyre maintained their integrity during a trans-pacific movement requiring 2–3 years. Further studies should reveal that the area of positive anomaly off the west coast of North America in 1958 may be traced westward back across the tropical Pacific Ocean, but these are beyond our resources at this time. We know, however, that the annual sea surface temperature maxima for 1953–60 off the west coast of Mexico occurred in 1959. These warm and cold areas, 180° out of phase, are believed to be quasi-permanent characteristics of the present day gyre.

The biological implications of being able to forecast the locations in time and space of such warm and cold areas in the ocean are almost limitless. Although sea surface temperature data can be averaged over smaller space and shorter time intervals for more finite investigations, there is obviously a limit to which this is effective because of the nature of these data. Semiannual means are useful in investigating relations with local fisheries phenomena. For example, 1953 and 1958 year classes of herring over-

whelmingly dominated the herring fishery of south-eastern Alaska for 5 and 4 years, respectively, and the 1955 and 1956 year classes were notably poor¹⁵. Temperature conditions during winter generally dictate conditions during spring when herring approach the coast to spawn. Monthly sea surface temperature data in the quadrangle off Queen Charlotte Islands (50–55° N, 130–135° W) are complete for October to March for 1949–66 and indicate that the two dominant spring spawning periods occurred following abnormally warm winter conditions (Fig. 4). Both sets of data are obviously subject to other constraints, but the apparent relation is worthy of further investigation. Further, Pacific salmon, numbered in millions, return to the Fraser River (British Columbia) system during summer and, in 1958, these Subarctic anadromous fishes approached the river around the north side of Vancouver Island instead of the south, a northward displacement of 250 km (refs. 16 and 17). At that time, the mean anomaly of sea surface temperature for April–September in the above quadrangle (which lies north-west of Vancouver Island) was a maximum of +1.7° C. Although the cause for the northward onshore migration route is not known, unusually warm ocean conditions were considered to be one factor.

Our evidence confirms the possibility of a high order of coherence in a generally turbulent oceanic regime. We hope that this will stimulate support for acquiring the oceanographic station data—from monitoring and research cruises, ships of opportunity, ocean stations, satellites, and oceanographic buoys—required to fully document and understand conditions and processes in the North Pacific gyre, and that it will accelerate interrelated biological and meteorological studies. Two plans have now been proposed: Cooperative Investigations of a Large Ocean Gyre (CILOG), and Cooperative Investigations for the North Pacific (CINOP).

These results were presented in part at a meeting of the Panel on Marine Environmental Observation and Forecasting of the US-Japan Committee on Natural Resources at the National Oceanic and Atmospheric Administration Headquarters, Rockville, Maryland, on November 20, 1972, and a meeting of US-USSR oceanographic exchange delegation at the NMFS Northwest Fisheries Center, Seattle, Washington, on December 5, 1972. We acknowledge the instigation and support of studies using ship of opportunity data by J. H. Johnson, NMFS Pacific Environmental Group, Monterey, California. We also thank S. E. Turner, R. E. Pearson, V. Fiscus, and M. Morey of the NMFS Northwest Fisheries Center for assistance.

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Mediterranean Plate Tectonics and Triassic Palaeogeography

ALFONSO BOSELLINI

Istituto Geologico dell'Università di Ferrara

K. J. HSÜ

Geologisches Institut, ETH Zürich

Well known features of the geology of Western Europe are reinterpreted in the light of the deep-sea drilling results and other recent data.

MANY years ago geometrical considerations led Argand to speculate that the genesis of the Mediterranean could be related to a eastward movement of Africa relative to Europe¹. Analysis of seafloor spreading in the North Atlantic indicated that this eastward movement of Africa occurred chiefly in the initial stage of the opening of the Atlantic, during the interval between 180 and 80 m.y. (refs. 2-4). Palaeomagnetic data indicate rotations of microcontinents⁵, such as the mid-Tertiary movement of Sardinia and Corsica^{6,7} and the chiefly Mesozoic counter-clockwise rotation of the Iberian block and of Italy⁸, when Africa was displaced eastwards relative to Europe. Attempts have been made to reconstruct the Triassic positions of the microcontinents prior to the opening of the Atlantic^{8,9}. These reconstructions were based on matching bathymetric contours. They were speculative, and contained inaccuracies which should be corrected. For example the northern margin of the African plate during the Mesozoic has been drawn through the Strait of Gibraltar. Yet geologists possess clear evidence that the Spanish Betic Cordillera and the Moroccan Rif were never far apart during the Mesozoic and Cainozoic¹⁰. This has been cited as evidence against the large movement of Africa, which was deduced on the basis of magnetic anomaly data in the Atlantic. More radical sceptics would proceed to the extreme and question the very essence of seafloor spreading theory.

Facies analysis is a time honoured geological method to test and modify palaeogeographical reconstructions. As the postulated movements of Europe relative to Africa did not start until Jurassic, a consideration of the depositional facies of the Triassic of the circum-Mediterranean regions should provide some clues if the reconstructions of microcontinents are contradictory to geology and if such contradictions could be resolved through a minor or a major modification.

Upper Triassic Facies

Triassic sedimentary rocks of Europe are traditionally divided into two facies: the German Triassic and the Alpine Triassic. The German type commonly occurs in Hercynian Europe and on the northern margin of the African block, whereas the Alpine type is characteristic of the Tertiary chains (Apennines, Alps, Dinarids, Carpathians and so on).

Exceptions are the Pyrenees, Atlas and northern Apennines, where the German Triassic prevails.

Post-Hercynian (Permo-Triassic) tectonic and palaeogeographic evolution of Southern Europe had a very characteristic feature: a subsiding area, principally marine, was present in the east (Italy, Balkans, Greece) and an apparently stable area, principally continental, was situated to the west (Iberian Peninsula, France, Sardinia, Germany). Marine transgressions were always directed eastward with lateral shifting of the various depositional environments and sedimentary belts. Consequently the Permian-Triassic facies of the central area are chiefly time-transgressive.

To construct an Upper Triassic facies map it is necessary to draw it "instantaneous" as much as possible. Unfortunately the Upper Triassic sediments, chiefly continental or paralic, have not yielded any marker-beds and a precise biostratigraphical correlation is not in every instance possible. We have chosen to depict the facies of the Norian and Keuper intervals, for the Alpine and German Triassic respectively, because they are approximately time-equivalent within the framework of present chronostratigraphic knowledge.

The map (Fig. 1) presented here, which grossly refers to the Keuper-Norian interval, is subdivided into the following facies:

(i) Continental facies (red beds) is represented by a red bed sequence composed of conglomerates, sandstones and shales. From the environmental point of view we envisage

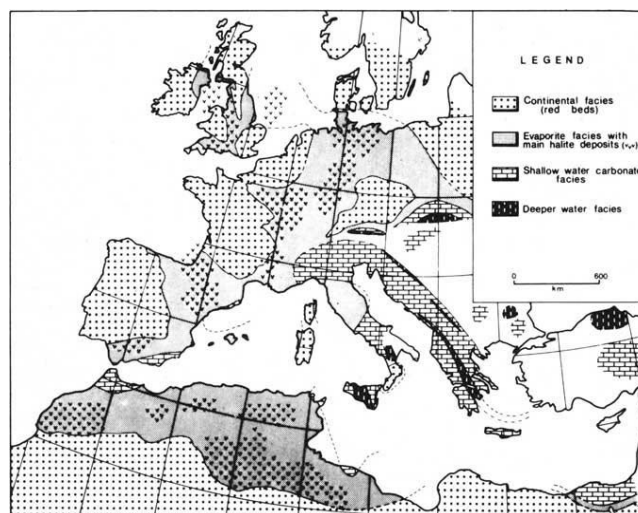


Fig. 1 Present distribution of Upper Triassic facies.

a great terrestrial semi-arid region with extensive fans dissected by braided streams, alluvial plains with meandering rivers in which point-bar sequences formed and interior depressions in which clayey and silty sediments accumulated. Prevalently denuded areas, covered with thin pediment deposits, are also included in the facies. They are the European Hercynian massifs, part of Scandinavia and the Sahara shield.

(ii) Evaporite-facies is the classic facies of the European Keuper, represented by varicoloured marls and shales, dolomite, gypsum, anhydrite and halites. This evaporite-bearing unit grades downward to paralic (Muschelkalk) or continental (Verrucano of Tuscany) sequences. Also the facies realm is intermediate between the continental facies and the shallow-water carbonate facies. Traditionally, the evaporites and associated sediments have been considered coastal deposits, on tidal flats or in restricted lagoons and gulfs. But as we shall mention later, the shallow-water Alpine Triassic, represented by the Hauptdolomit facies of the Engadine and the Dolomites, has also been interpreted as a tidal-flat or sabkha facies^{11,12}. Why should evaporites occur in one coastal region but not in the other?

Drilling in the Mediterranean led us to recognize the possibility that large inland seas could be partially or completely desiccated, evaporites could be deposited in inland desert basins whose floors could be hundreds or even a few thousand metres below sea level¹³. Triassic desert basins possibly developed in regions of continental crust during a relative orogenic quiescence (Hercynian orogeny more than 250 m.y. BP). Those basins were not likely to be as deep as the desiccated Mediterranean in late Miocene. Nonetheless, this interpretation offers an explanation for a long-standing puzzle concerning the widespread occurrence of the sabkha facies in the German and Alpine Triassic. If this unorthodox interpretation is correct, the Triassic sabkhas were not all coastal sabkhas, or tidal flats, some may have been continental sabkhas, or playa flats. A modern analogue would be the Death Valley or Salton Sea. Rise and fall of water levels within such evaporite basins would have been governed chiefly by drainage and climatic conditions, and not by the gravitational pull of the Sun and Moon.

The important occurrences of halite are also shown on the map. Salt basins are either situated within typically continental realms—Lorraine, Paris Basin, Ebro Valley, Rhine Valley, Northern Germany, North Sea and Irish Sea—or are present bordering continental facies—Northern Africa, Guadalquivir Valley, Aquitan Basin and Rhone Valley.

The distribution pattern of the halite suggests the presence of inland standing bodies of water, and strongly supports our interpretation of evaporite-deposition in inland basins.

(iii) Shallow water carbonate facies. The bulk of the Alpine Triassic is not a deep water sediment, but a shelf-carbonate facies. These limestones and dolomites can again be divided into two facies:

The first, always proximal to the evaporitic facies, consists predominantly of laminated, often stromatolitic, dolomites. Pisolitic horizons have been recognized in many areas, whereas locally the rocks are black and bituminous. This subfacies is typically represented by the Hauptdolomit of the Alps. The second, more marine subfacies is constituted by limestones and dolomites bearing Megalodonts and Foraminifera; laminations are quite subordinate. Patch reefs occur on the shelf margins, in front of the deeper basins. This subfacies is typically represented by the Dachsteinkalk of Austria and Yugoslavia.

The depositional environment of the shallow water carbonates was a vast shelf of "tidal flats" and lagoons, the flats prevailing in the landward regions. Climate was sufficiently arid so that pisolitic soils (or caliche), could be formed. The influence of the sea is recorded by the

bituminous rocks (Seefeld Schiefer of Austria, ichthyolitic shales of Southern Alps and Southern Apennines) which may have been laid down in tidal marshes and restricted inland basins. Typical regions for the shallow water carbonate facies are the Alps, the Dinarids and the Central-Southern Apennines.

(iv) Deeper water facies. Known in the Alps as Halstatt facies, the deep water Alpine Triassic is represented by cherty, micritic, radiolarian limestones with thin-shelled pelecypods (*Halobia*) and by scattered occurrences of *Ammonitico rosso*—the red nodular pelagic limestone rich in Ammonites, typical of the Tethyan geosyncline. The deeper water facies occurs in Sicily, Southern Italy, Austria, Yugoslavia, Greece and West Carpathians. In Northern Turkey and in Bulgaria terrigenous flysch-like sequences have also been reported.

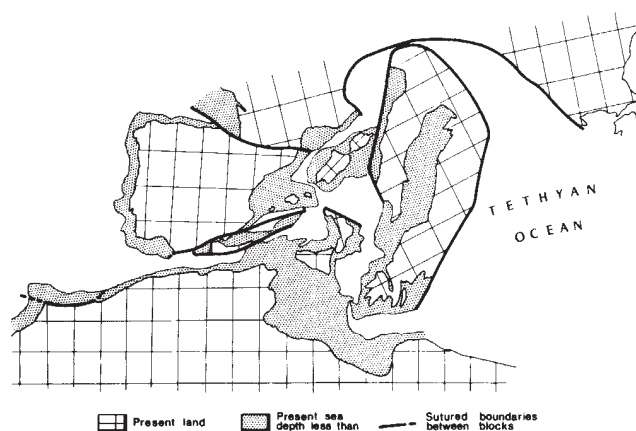


Fig. 2 Postulated reconstruction of Mediterranean microcontinents.

The pelagic cherty limestones were probably deposited in deep and narrow straits, sounds and oceanic tongues which subdivided the outer part of the vast shallow water carbonate shelf.

Distribution of Facies

The map of present distribution of Triassic facies shows several remarkable anomalies. While the stable Hercynian Europe (England, Germany, France, Spain, etc.) and Africa are practically characterized by two facies only (continental and marginal), the Mediterranean countries—notably Italy—present the entire variety of the Upper Triassic facies. These facies, moreover, are now very close to one another and randomly arranged. Typical examples of this situation occur in Southern Italy, where the deeper water facies of Lucania abut against the Calabria block; in Sicily, where the cherty limestones are localized between two continental massifs (Sardinia and Calabria); and in the Northern Calcareous Alps, where the deeper water Hallstatt facies is quite close to the Bohemian massif. The position of the Rif-Betic carbonate facies poses particular problems. The facies similarity between the Rif and Betic Cordillera has been the principal argument against large lateral movement across the Strait of Gibraltar. We note further that the Rif-Betic chief carbonates seem to have been misplaced as they are surrounded by continental or near continental facies.

These anomalous facies distributions can be partly restored taking into account the horizontal displacements (nappes) which occurred during the Alpine orogenesis (for example the Northern Calcareous Alps, the Calabria nappe and so on). Other anomalies must be explained by assuming some rotation and displacement of the Mediterranean microplates.



Fig. 3 Distribution of Upper Triassic facies, plotted on a map of postulated reconstructed palaeogeography.

Palaeogeographical Reconstructions

Figure 2 shows a reconstruction of the position of microcontinents during the Triassic slightly modified from that made by one of us two years ago⁹. A slight modification involves the position of Calabria, which should be detached from the rest of Italy, as suggested by the presence of ophiolites along the postulated sutured boundary. A major change concerns the northern boundary of Africa which is drawn south of the Rif province. In our revised reconstruction, we recognize a Rif-Betic (or Alboran) microcontinent, and place this unit farther to the east to account for its Triassic carbonate facies.

Figure 3 shows the distribution of Triassic facies on the reconstructed Triassic palaeogeography. The pattern permits a logical explanation. On the east was the Tethyan Ocean, which wedged out to the west as the Bullard fit of Pangea indicates. We recall that the extensional tectonics resulting ultimately in the opening of the Atlantic had already started in the Late Triassic, when block faulting was beginning to dissect the continent.

Basins and ranges like those in the present western United States were formed by rifting in the continental interior, where the Newark Series in North America and the New

Red Sandstone and its equivalent in Europe and Africa were deposited. On the more marginal parts of the continent, the basins were underlain by thinner crust and therefore deeper basin floors. Those basins were periodically submerged under marine waters, producing bituminous shales and euxinic sediments. But when they were isolated from the Tethyan Ocean by reefs and shelf carbonates of the Alpine Triassic, desiccation of inland seas led to evaporite deposition in salt lakes and on continental sabkhas.

Because the clastics from the continental interiors were trapped by evaporite-basins, the continental margin facing the Tethys was the site of carbonate deposition and reef growing, separating coastal sabkhas from the sea. Farther out, block faulting of continental margin associated with carbonate upbuilding produced a series of offshore basins and banks, and a topography similar to the continental borderland offshore southeastern United States (Florida-Bahamas) today. This Triassic continental borderland was the site of pelagic sedimentation.

We recognize the intricate situation of geological record and the imperfection of our knowledge. Nevertheless, we believe our facies approach supports a previous attempt to reconstruct Triassic palaeogeography which was based chiefly on the matching of bathymetric contours and brings new evidence for a more correct plate restoration of the Mediterranean region.

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LETTERS TO NATURE

PHYSICAL SCIENCES

Some Identifications of Radio Sources with Neutral Stellar Objects

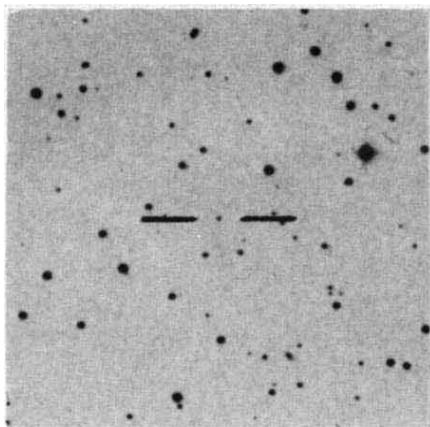
We present twenty-four identifications of radio sources with neutral coloured objects of stellar appearance. We consider these objects to be of special interest because they do not fall into the two normally accepted categories for identification; that is, galaxies or blue stellar objects. Two of them have recently been found to have exceptionally high redshifts^{1,2}, and it is hoped that further optical measurements on the others will produce equally interesting results.

The identifications are based on radio positions measured with the interferometer of the Royal Radar Establishment in the manner described by Adgie *et al.*³, and optical positions measured from prints of the Palomar Sky Survey. The

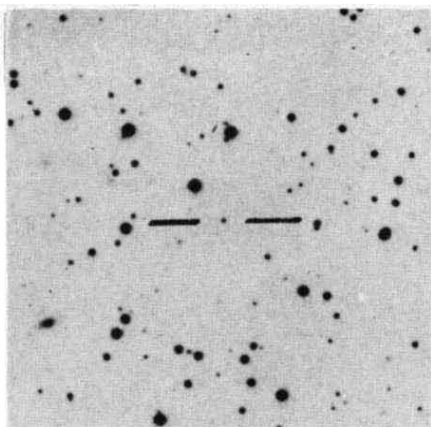
accuracy of the positions is such that reliable identifications can be made on the basis of agreement in position without regard to the appearance of the optical object. With less accurate positions, a definite identification with a neutral stellar object is not possible because of the high probability of a coincidence with a normal star^{4,5}.

Several different programmes of identification work have been carried out and the results are being prepared for publication elsewhere. From these, we have selected this small group of sources which appear to us to be indistinguishable from stars on the Sky Survey prints and are neutral in colour; some have been included which appear to be slightly red or slightly blue, but very blue objects are certainly excluded.

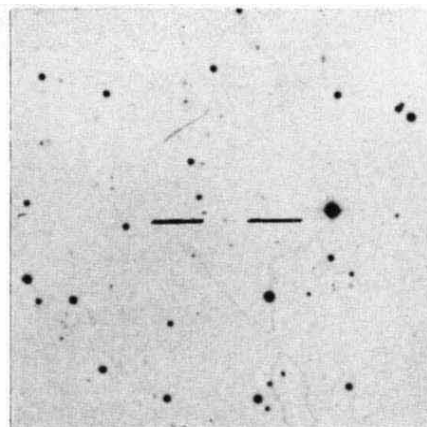
The twenty-four sources are listed in Table 1. With the exception of PKS0735+17 all the optical positions have been measured by us from the Sky Survey prints using, in each case, about ten stars from the AGK2 catalogue as a reference. The



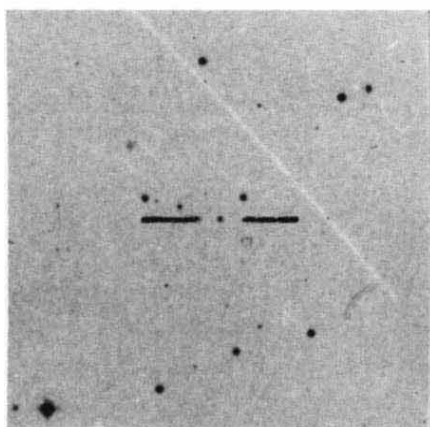
OB338
(O)



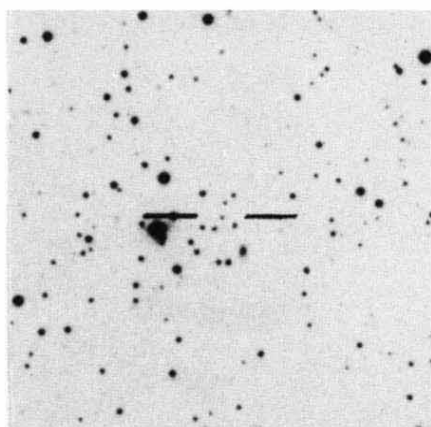
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(E)



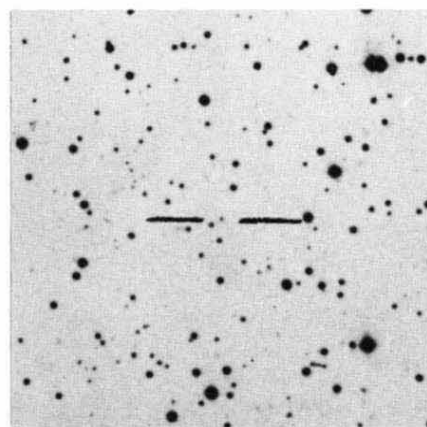
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(E)



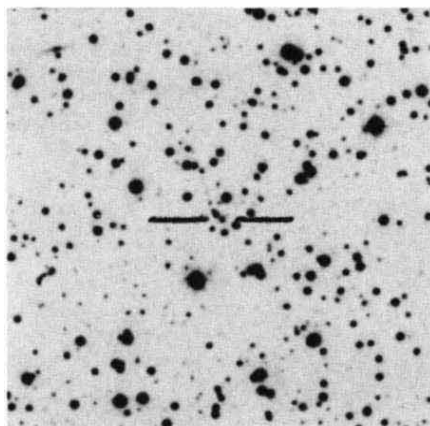
OD094-7
(O)



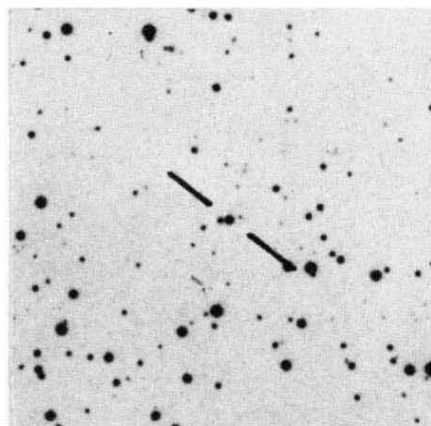
OG050
(E)



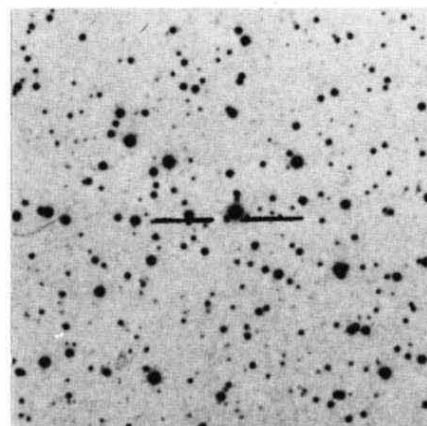
OH471
(E)



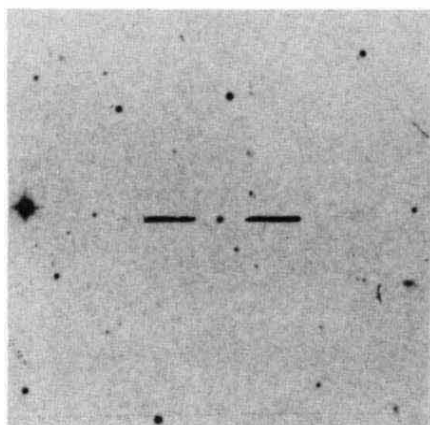
OI-039
(O)



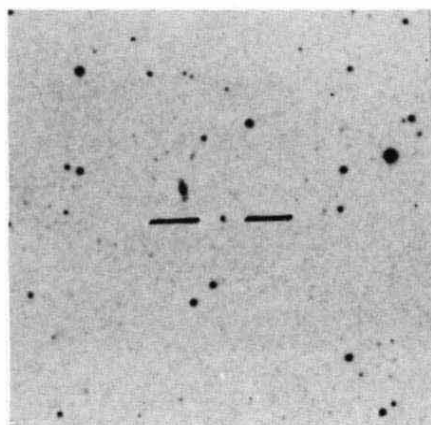
PKS0735+17
(E)



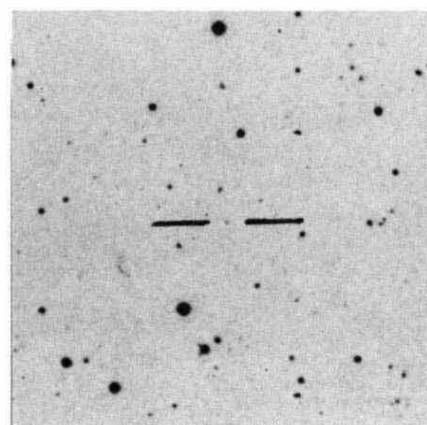
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(E)



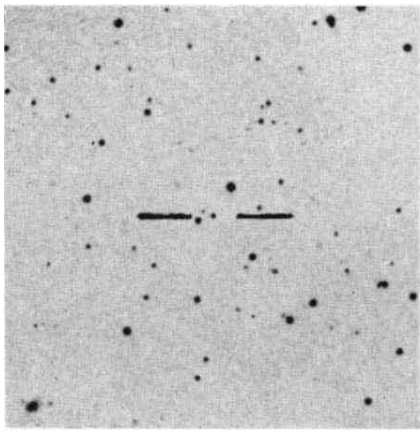
OM133
(O)



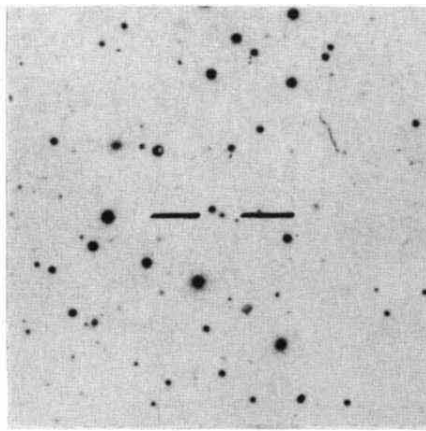
PKS1134+01
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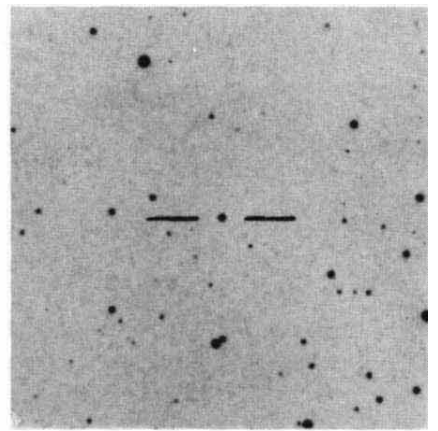
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(E)



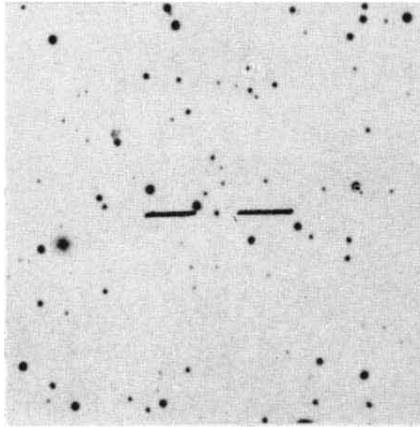
OQ172
(E)



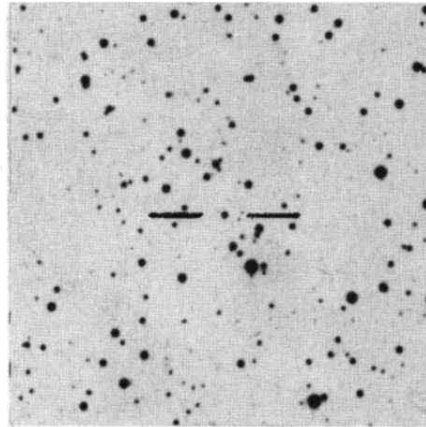
PKS1509+022
(E)



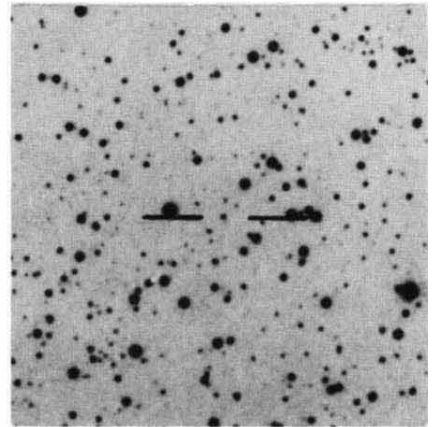
GC1514+19
(O)



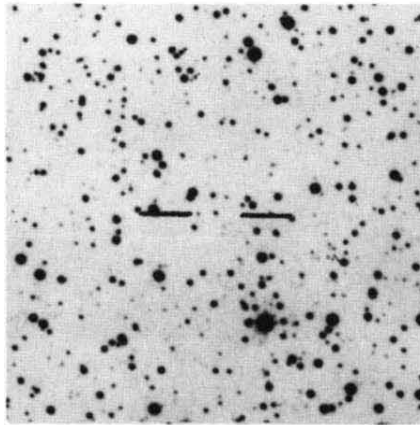
O5108-2
(O)



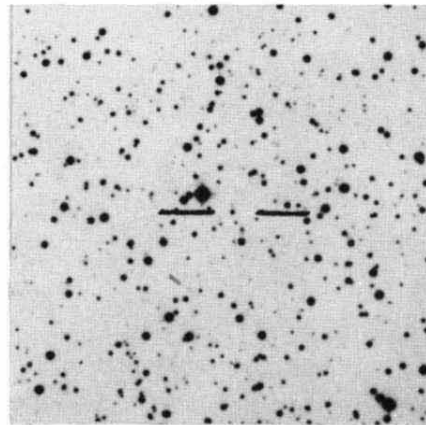
OS094
(E)



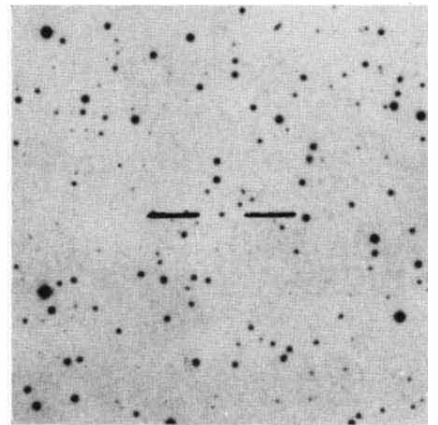
OT081
(O)



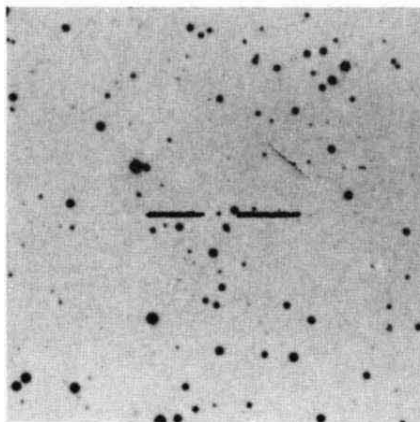
OV591
(E)



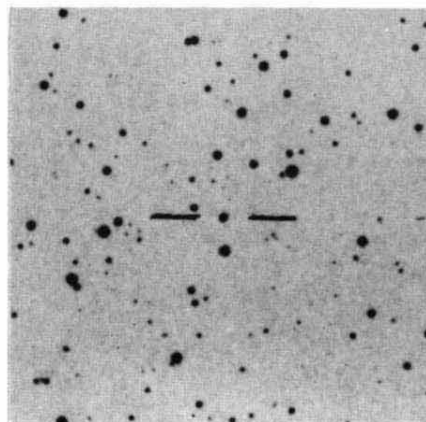
OW538
(O)



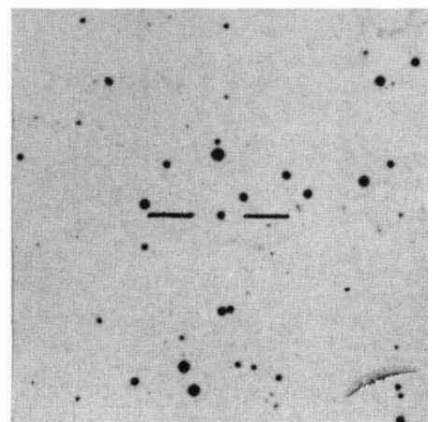
OX036
(E)



OX161
(O)



OX169
(O)



OY091
(E)

Table 1 Positions and Optical Magnitudes of Sources Identified with Neutral Stellar Objects

Source	Right ascension		RRE radio position (1950.0)		Declination		Error $\pm''$	Optical-radio position		Optical magnitude*	References to previous identification	Notes
	h	m	s	Error $\pm s$	°	'		$\Delta\alpha$ s	$\Delta\delta$ "			
OB338	00	24	02.78	0.05	34	52	07.1	0.6	-0.01	-0.4	19	—
GC0035+36	00	35	04.39	0.07	36	42	43.3	0.6	+0.08	-0.9	18.5	—
OD058	02	34	59.95	0.04	09	06	03.8	0.6	-0.01	+0.6	19.5	11 Slightly red
OD094.7	02	56	47.00	0.06	07	35	46.2	0.7	0.00	-0.9	18	12 Slightly red
OG050	05	29	56.48	0.03	07	30	38.7	0.4	0.00	-0.2	19	— Slightly red
OH471	06	42	53.26	0.16	44	54	32.7	1.0	-0.19	-1.7	19	11, 13 $z=3.40$ (ref. 1)
OI-039	07	23	17.86	0.05	-00	48	54.6	0.7	-0.01	-0.5	18	—
PKS0735+17	07	35	14.11	0.03	17	49	09.4	0.3	-0.031 [†]	+0.06 [†]	16.5	7, 14 Slightly blue
OI-072	07	43	21.06	0.05	-00	36	55.0	0.6	+0.02	-0.6	17.5	10, 12
OM133	11	19	52.21	0.04	18	21	54.1	0.4	+0.03	+0.1	18	—
PKS1134+01	11	34	55.72	0.09	01	32	50.1	1.3	-0.01	+0.7	18.5	— Slightly red
PKS1427-01	14	27	14.24	0.11	-00	59	32.4	1.6	-0.11	-0.9	19.5	—
OQ172	14	42	50.48	0.03	10	11	12.4	0.3	-0.04	-0.6	18.5	5, 8, 14 $z=3.53$ (ref. 2), slightly blue
PKS1509+022	15	09	43.90	0.09	02	14	28.3	1.3	-0.05	+2.4	18.5	—
GC1514+19	15	14	40.97	0.05	19	43	10.9	0.5	+0.05	+0.8	17	— Slightly blue
OS108.2	16	04	49.38	0.06	15	59	33.1	0.6	+0.06	-0.8	18	—
OS094	16	56	05.62	0.04	05	19	46.8	0.5	+0.06	-0.1	17	5 Slightly blue
OT081	17	49	10.39	0.03	09	39	43.2	0.4	+0.01	+0.1	18	12 Slightly red
OV591	19	54	22.82	0.17	51	23	46.5	0.9	-0.36	-0.1	18.5	— Misidentified in ref. 11
OW538	20	22	38.05	0.21	54	17	49.6	1.0	+0.45	-0.4	18	— Slightly red, misidentified in ref. 11
OX036	21	21	14.77	0.03	05	22	27.3	0.4	+0.03	-0.1	18.5	—
OX161	21	36	37.37	0.03	14	10	00.4	0.5	+0.09	+0.2	18.5	9 Misidentified in ref. 11
OX169	21	41	13.77	0.05	17	30	02.2	0.6	-0.03	-0.2	16.5	— Slightly blue
OY091	22	54	45.98	0.04	07	27	09.8	0.5	+0.02	-0.9	17	12 Slightly red

* Optical magnitudes have been estimated from the Sky Survey prints.

† From an accurate optical position measured by Couper¹⁵.

error on these optical positions is about 0.6 arc s r.m.s. This was estimated from the observed differences between our optical and radio positions (accurate to about 0.5 arc s r.m.s.) for a large number of identifications. All the listed radio positions were measured with the RRE interferometer, though for some of them the maximum spacing was not used and the accuracy of their positions is therefore not so high. Nevertheless, it is considered that the chance of an accidental identification with a normal star is still quite small. For the two sources PKS0735+17 and OX161 the previously published accurate radio positions^{7,9} are in good agreement with those measured at the RRE.

We give finding charts for all the objects in the figures. They are enlargements from the Sky Survey prints, with a scale of 10 arc s mm⁻¹. Those charts copied from the blue prints are marked (O) and those from the red (E). Some of the finding charts have been given elsewhere, but they are repeated here for convenience and also to remove any ambiguities that could arise from tentative identifications made on the basis of inaccurate positions.

It is interesting that, of the many sources we examined, those with flat, peaked or inverted radio spectra gave the highest yield of identifications with neutral stellar objects. In fact, most of the twenty-four selected sources have spectra of this type. This leads us to expect that the radio emission from these sources comes from very compact regions, and may well be variable⁶.

We can only speculate on the results to be revealed by optical spectroscopy. The measurement of redshifts in excess of 3 for OH471 (ref. 1) and OQ172 (ref. 2) leads us to suggest that some more of our selected sources might similarly be quasars with very high redshifts. An alternative possibility is that some of the objects may be found to have featureless spectra and thus belong to the small class of objects similar to BL Lac.

We thank Mr N. J. McEwan who took part in one of the identification programmes. J. H. C. thanks Sir Bernard Lovell for support from the Nuffield Radio Astronomy Laboratories, Jodrell Bank, and R. L. A. acknowledges a Royal Society research fellowship supported by the Weir Foundation.

I. W. A. BROWNE

University of Manchester,
Nuffield Radio Astronomy Laboratories,
Jodrell Bank

J. H. CROWTHER
R. L. ADGIE

Royal Radar Establishment,
Great Malvern,
Worcestershire

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Formation of the Emperor Seamount Chain

THE Pacific ocean basin is attributed to a single, continuously active ridge system which is believed still to be active today in the eastern Pacific, although much of the eastern flank of the ridge and parts of the ridge itself have been subducted into a fossil trench along the west coast of North America and active trench regions such as the Aleutian trench and the Peru-Chile trench. One problem with this model is the present activity on the island of Hawaii, which according to the model is sitting in the centre of a stable plate. One explanation is based on Wilson's proposal¹ that the linear ridges in the Pacific were formed as the crust moved over a localized "hot spot" in the asthenosphere or upper mantle, but the physical problems involved in creating and maintaining such localized "hot spots" over millions of years have largely gone unanswered. Although a few workers remain sceptical (see ref. 2), acceptance of the theory has been widespread.

Here I propose that the crust of the north Pacific developed in at least two distinct stages. I suggest that the Emperor Seamount chain formed along the boundary between an old stable portion of ocean crust and an active spreading ridge migrating parallel to the boundary, with resultant left-lateral strike-slip motion along the axis of the chain.

Magnetic surveys conducted in the north Pacific have revealed linear seafloor spreading anomaly patterns (Fig. 1). Heirtzler and others³ have correlated the anomalies east of the Emperor Seamount chain with the north Pacific reference profile, and have assigned the ages shown. Hayes and Pitman⁴ have described the anomalies west of the Emperor Seamount chain. They found no correlation between those anomalies and the north Pacific reference profile, leading them to conclude that the seafloor there was generated before Middle Cretaceous time (110 m.y. BP). Larson and Chase (unpublished) have also inferred a lower to middle Cretaceous age for the crust west of the Emperor Seamount chain, based on magnetic studies. The older age of crust in the western Pacific has been confirmed by the findings of the Deep Sea Drilling Project^{5,6}. The model presented here requires only that that portion of seafloor is older than 110 m.y.

In Fig. 2 I present a possible tectonic interpretation of the magnetic patterns in the north-west Pacific. The ridge system position is shown as it is today and sequentially back to 110 m.y. BP, based on extrapolating the anomaly sequence backwards assuming a constant rate of spreading between principal fracture zones. I also assume that the older seafloor west of the Emperor-Hawaiian ridge system remained stable relative to the seafloor to the east.

I suggest that the Emperor Seamounts may have formed as a result of extrusion induced by strike-slip motion, interaction between stable ocean crust and the migrating ridge, and/or secondary activity along a zone of weakness created by the former boundary. The first would require that the ages of the seamounts be consistent with the time of motion. The second requires that they be younger to the north, consistent with the age of the ridge migration; this implies that the chain may be younger to the north, rather than older—as the "hot spot" theory predicates. And the third requires that they be subsequent to that of the active boundary. The last of these would allow ages consistent with the "hot spot" theory. The point being made here is that a "hot spot", if indeed one does exist, is directed wholly or in part by previous tectonic features, and not simply by plate motions relative to the "hot spot".

It is interesting that Fisher *et al.*⁷ have proposed another origin for linear oceanic ridges which does not necessitate a "hot spot" mechanism, that is, several aseismic ridges located in the Indian Ocean may have originated during reorientation of the spreading axis, causing former transform faults to widen, and resulted in extrusion.

Data on the ages along the Emperor Seamount chain are almost non-existent at present. Ozima *et al.*⁸ obtained K-Ar ages for three samples dredged from the top of the Suiko seamount (44° 33' N, 170° 17' E) of 41.8 m.y., 40.4 m.y., and 21.2 m.y. The unique character of these samples (two identified as pyroxene andesite and one as metamorphosed basalt) in the seamount environment led them to conclude that the ages obtained probably do not represent the age of the seamount. Clague and Dalrymple⁹ have obtained a date of 46.4 ± 1.1 m.y. BP for the Kōko seamount, located just north of the Hawaiian-Emperor bend, based on seven samples (two sanidine trachytes, four basalts, and a phonolite). The only other reported date

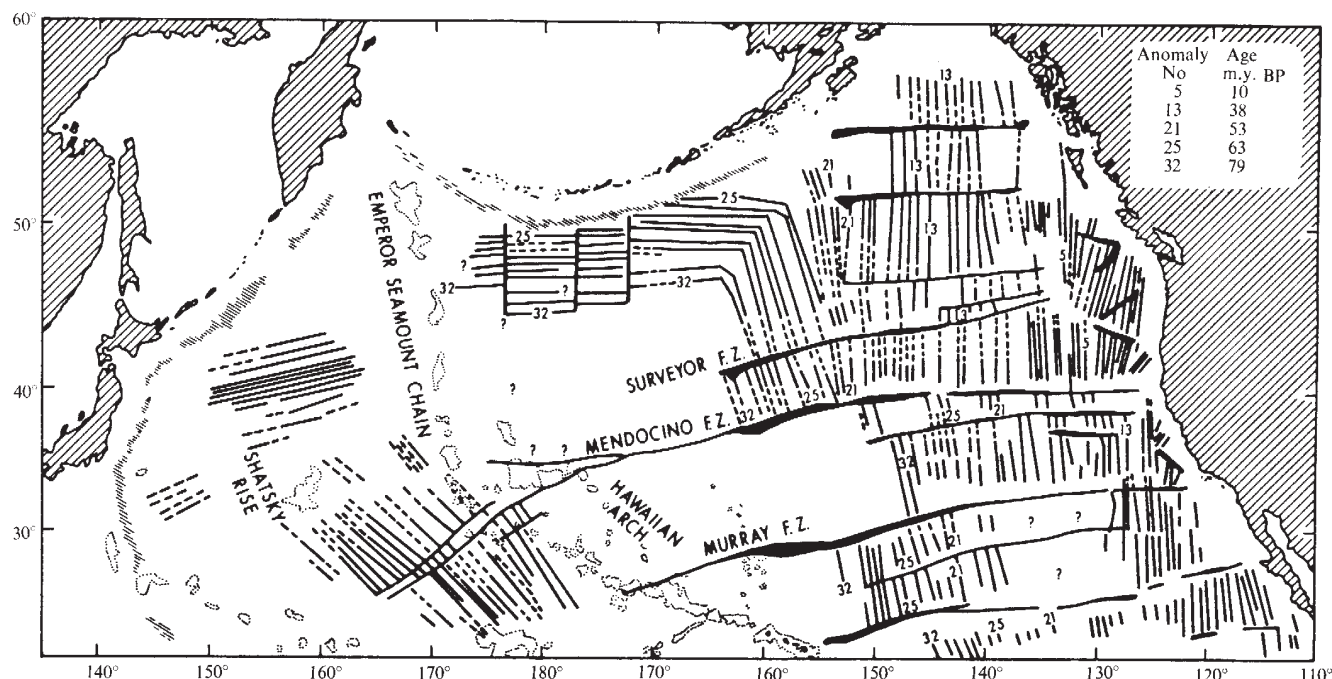


Fig. 1 Magnetic anomaly lineations in the north Pacific. The anomalies in the north-east Pacific have been described by numerous workers. Numbered anomalies have been correlated to the North Pacific Reference Profile and the ages are shown in the inset. According to Hayes and Pitman⁴, the patterns in the north-west Pacific seem to be much older than those to the east (map modified from ref. 4).

for the Emperor Seamount chain is that from the Deep Sea Drilling Project which drilled on the northernmost seamount of the chain⁶. There the drilling bottomed in pyroxene-plagioclase diabasic basalt of middle Maestrichtian age (68 m.y.).

No such strike-slip motion occurred along the Hawaiian Islands ridge, because the orientation of the spreading ridge would have had to parallel the present trend of the ridge. No evidence of fracture zones associated with the Hawaiian ridge south-east of Hawaii has been found, supporting this contention. Also, the recent ages of the Hawaiian Islands do not support primary genesis, but subsequent activity along a zone of weakness resulting from a quiescent boundary. I propose that the bathymetric continuity of the Emperor chain with the Hawaiian ridge is the result of both features

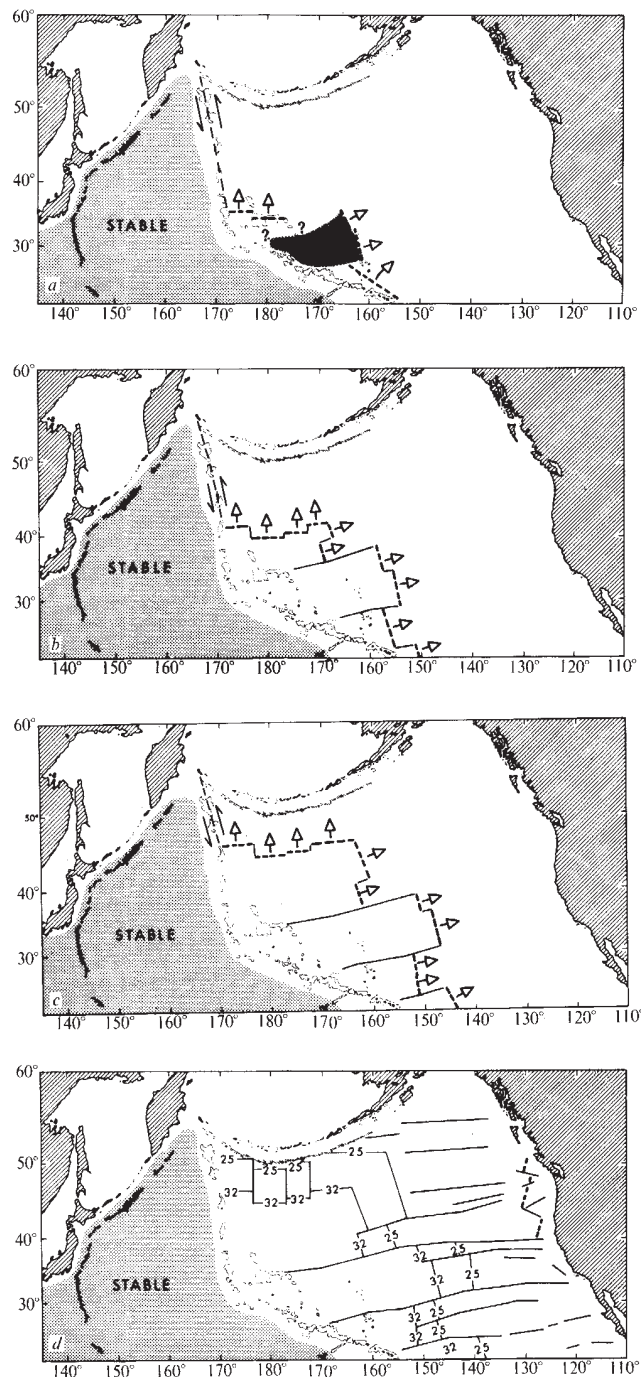


Fig. 2 Reconstructed ridge positions from backward extrapolation of the known anomaly positions shown in Fig. 3. Heavy dashed lines are ridge positions at, a, 110 m.y. BP; b, 95 m.y. BP; c, 79 m.y. BP; d, present.

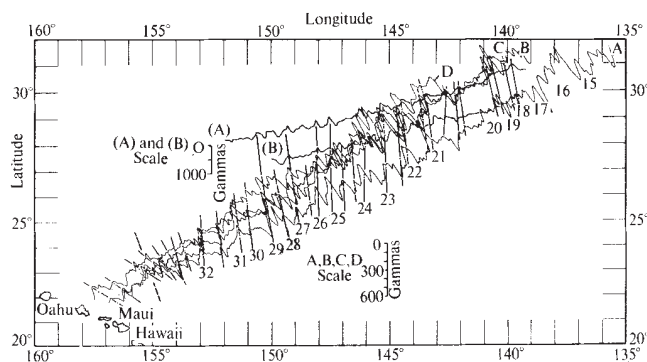


Fig. 3 Magnetic lineations east of the Hawaiian Islands. Note apparent change in trend from NW-SE to N-S before anomaly 32 (79 m.y. BP) (from ref. 10). Magnetic anomalies are numbered.

forming on a continuous boundary. Details of the mechanism involved and the formation of the Hawaiian ridge will be discussed elsewhere.

The gap in the reconstructed ridge along the Mendocino fracture zone (Figs 1 and 2a) may indicate an original offset in the ridge or may represent a tectonic offset caused by secondary east-west spreading in the shaded area. In any case, the offset seems to have occurred before 79 m.y. BP because the offset is present in matching anomaly 32 across the Mendocino fracture zone. The origin of the offset along the Murray fracture zone is not clear, but must be tied to the explanation of the "disturbed zone" south of the Murray fracture zone between 130° and 140° W. The primary or secondary nature of these two offsets might also relate to the reported extensions of the two fracture zones into the north-west Pacific, proposed here to have been stable relative to the renewed crustal generation to the east. Origin of the other fracture zones in the north-east Pacific may be due to original ridge offsets or later readjustments of the ridge system as it migrated north and east. Formation of the Emperor trough would then have postdated the formation of the basin east of the Emperor Seamount chain.

Finally, magnetic data published by Malahoff and Handschumacher¹⁰ indicate that the ridge has undergone reorientation from a north-west-south-east trend to a north-south trend east of the Hawaiian Islands before anomaly 32 (79 m.y. BP) (see Fig. 3).

The model presented here assumes that the north Pacific ocean basin has not always been a homogeneous plate, although it appears so today. If the boundary discontinuities I suggest are correct, the Line Islands south of the Hawaiian ridge and other linear features may also be related to episodic genesis of the Pacific crust. Moreover, the western Pacific basin may have evolved from tectonic activity which was partially or wholly unrelated to subsequent events involving the ridge system in the eastern Pacific.

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DAVID HANDSCHUMACHER

Hawaii Institute of Geophysics,
University of Hawaii,
Honolulu, Hawaii 96822

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Lateral Heterogeneity in the Deep Mantle from Seismic Body Wave Amplitudes

HERE we describe some seismic short-period body-wave amplitude anomalies observed in the United States. These anomalies are particularly large for ray paths which travel close to the core-mantle boundary and may provide another way of looking for anomalous structure in this region.

Observations of short period seismic P waves over many years have established that the amplitude as observed from the same event in the distance range from 30°–85° varies remarkably little^{1,2}. Beyond 85°, however, the amplitude declines steadily to be down by an order of magnitude at 100°. At some distance in the vicinity of 100°, rays from source to receiver intersect the core-mantle boundary, and because the velocity of P waves is less in the core than at the base of the mantle, beyond this distance there is a shadow. The shadow³⁻⁵ is weakly insonified by waves that have presumably diffracted around the core-mantle boundary. The characteristics of diffracted P waves vary from path to path and there must be lateral variations in elastic properties deep in the mantle sampled by diffracted P waves⁵.

If that is so, another piece of data which might map heterogeneities rather precisely would be amplitudes of signals in the vicinity of the shadow. It is difficult to define the shadow distance precisely as the steady decline from 85° obscures the

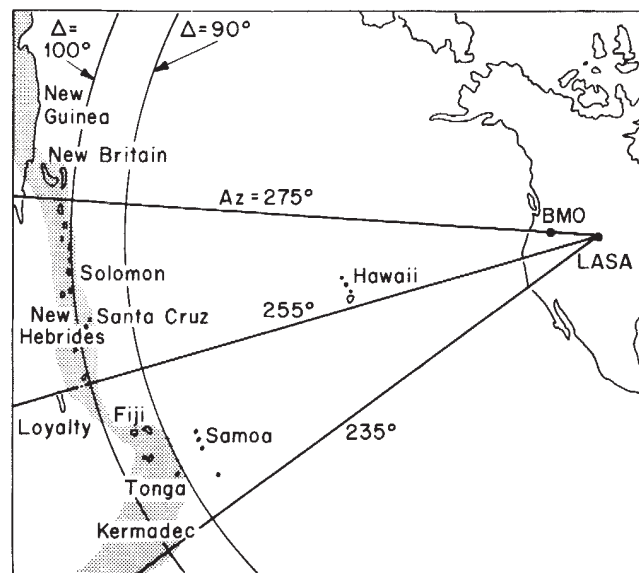


Fig. 1 Azimuthal, equidistant projection of the Pacific centred on LASA. The Blue Mountains Observatory (BMO) is also shown. The seismic belt around the South-West Pacific is shaded.

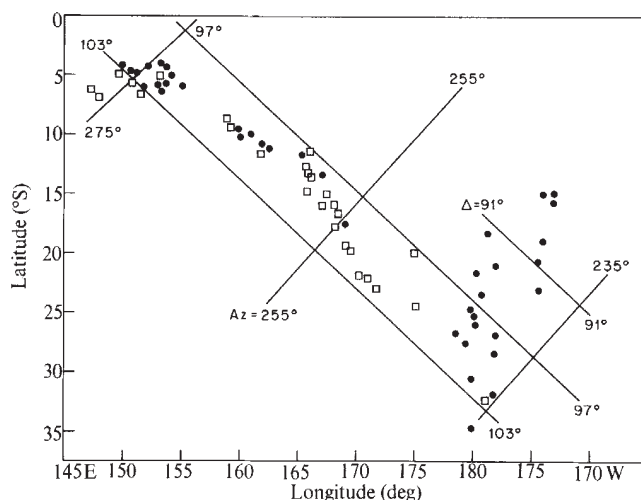


Fig. 2 Location of earthquakes of $m_b > 5.0$ used in this study. ●, Normalized amplitude > 1 nm; □, signal ≤ 1 nm, or absent.

phenomenon, so rather than look for a precise distance to the shadow we shall display amplitudes as recorded at LASA as a function of geographical location in a distance range from 85° to 105° for the 40° of azimuth covered by the seismic belt Kermadec–Fiji–Tonga–New Hebrides–Solomon Islands–New Britain–New Guinea (Fig. 1). Although the coverage is not uniform it is sufficient to see some salient features.

We examined the LASA bulletin and the Earthquake Data Reports (EDRs) of the US National Ocean Survey for a period of 7 months from February to August 1972. For every earthquake in this sector reported in the EDR, the LASA bulletin was searched for a detection. The amplitude of the signal at LASA was recorded. The usual seismic convention is to report the largest zero to peak amplitude within the first three or four cycles of signal, even if the later signal is much larger. Because the LASA amplitude is determined automatically we took care to ensure that automatic and visual determinations of amplitude were in agreement. The straight amplitude was used rather than the amplitude/period ratio.

We then normalized reported amplitude to that expected if the event were of $m_b = 5.0$. Only events of $m_b \geq 5.0$ were considered at this stage, because the magnitude reported in the EDR for smaller events generally comes from less than five stations, one of which is usually LASA, the station at which we are looking for amplitude anomalies. The results are summarized in Fig. 2. The 90% cumulative threshold for events reported in the LASA bulletin is around 1 nm (ref. 6), so with a certain amount of statistical precaution we can assert that unreported events have signals of less than a nanometer. To the extent that reciprocity is valid, Fig. 2 could be regarded as a condensed plot of the amplitude distribution in the South Pacific from a magnitude 5.0 earthquake at LASA. Equidistant contours from LASA are also drawn and demonstrate clearly the azimuthal variation in amplitude. It is possible to "see" to at least 102° both in the Kermadec and New Britain regions, but seismic visibility is limited to about 97° in the New Hebrides.

Because there is such a strong correlation of visibility with region at the 1 nm level we have taken care to ensure that nothing within the automatic detection process (such as inadequate beam coverage during the real time search) is generating the anomaly. Seismograms were scanned visually, and LASA bulletins from other time periods, when the system was operated differently, were examined but the effect persisted. Indeed it was first noted by Needham⁷ when LASA detection operations were much less automatic.

Lateral variations in reported amplitude could arise from anomalies in the receiver region, in the upper mantle beneath the source and along the path through the deep mantle. The

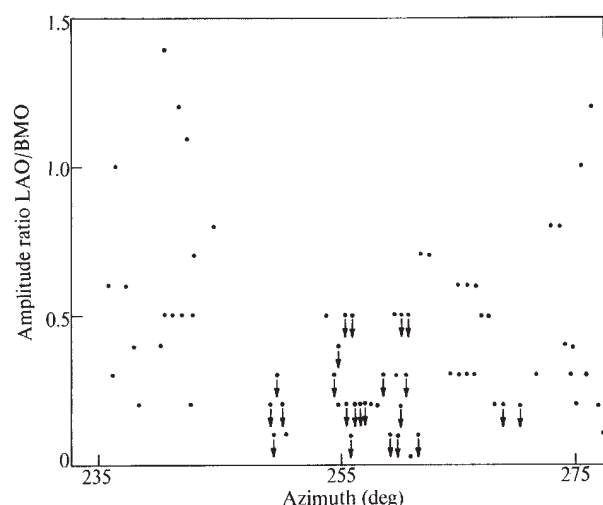


Fig. 3 Amplitude ratio of signals at LASA to those at BMO in the distance range 97° – 101° as a function of azimuth. Arrows attached to a dot indicate that no signal was seen at LASA and so the value is probably less than that given (which corresponds to the 1 nm detection threshold).

first, sub-receiver anomalies, are the easiest to discount. Although amplitude anomalies arising from crustal heterogeneity are frequently observed, the anomaly seen here repeats itself at all 340 seismometers of the array, which would necessitate a rather implausible crustal structure.

The second possible reason for anomalies, structure beneath the events, is less easy to dismiss. We assume for discussion that it is the New Hebrides earthquakes which give anomalously low amplitudes rather than the remainder giving anomalously high amplitudes. A nodal plane in the focal mechanism could cause low amplitudes, but the effect is seen on many earthquakes at differing locations, the mechanisms of which will be sufficiently varied to minimize such a phenomenon. A more plausible source of amplitude reduction could be the presence of a dipping slab in the New Hebrides, with dip and strike such that seismic rays to LASA from events at its top would have to traverse its length. Davies and Julian⁸ have shown the effect such slabs can have on short period seismic signals by casting a shadow into the teleseismic field. But the effect is seen for a wide variety of events in different positions relative to the slab (including deep events), and ray tracing calculations predict that the shadow will depend strongly on the location of the event with respect to the slab. Further, LASA sees no better the surface reflected phase pP which follows a completely different path in the vicinity of the source. We are thus confident that we are not seeing a slab effect. Similar considerations would apply to amplitude reduction by a zone of high attenuation. But it is possible to establish an even better case by considering amplitudes reported by another station relatively close to LASA. The Blue Mountains Seismological Observatory, Oregon (BMO), is a high quality small array reporting regularly to the US National Ocean Survey. It is in approximately the same azimuth as LASA to the South-West Pacific, but the distance is shorter by about 8° . In terms of emergence angle at the source this represents a degree, at most, in dip angle. Thus rays to BMO and LASA would sample the same source heterogeneities. By comparison of BMO and LASA amplitudes we should get a clear indication of whether the low amplitudes from the New Hebrides region are a source region phenomenon.

In Fig. 3 we plot the ratio of LASA to BMO amplitudes for the distance range 97° – 101° as a function of azimuth. When BMO has reported a detection and LASA has not we have assumed that the signal at LASA was less than 1.0 nm and have put an arrow under the point, to indicate "less than". Exactly the same pattern appears—we note the many arrows

between 245° and 260° —and we conclude that the effect is deeper in the mantle and laterally confined within these azimuths. The amplitude suppression seems to be at least a factor of three.

The BMO data by themselves show no obvious sign of amplitude suppression, and so it is appealing to attempt to confine even further the extent of the anomaly. For instance, if the anomaly were a velocity perturbation right at the core/mantle boundary somewhere along the ray path, signal to LASA could be grazing the boundary (in a spherically symmetric Earth) whilst that to BMO was passing 100 km overhead⁹. The lack of a BMO anomaly could be construed as indicating that the anomalous region, whatever it may be, is confined to the bottom 100 km of the mantle. Care is needed in making such an assertion, however, because the presence of the low velocity core ensures that any rays to LASA which attempt to get round this anomaly by descending (on a least time path) to a deeper level are refracted into the core, whereas the same is not immediately true at shallower depths. A ray-tracing programme gives insights into ray behaviour in the vicinity of velocity anomalies, but the details of the models used control the expected amplitudes very strongly.

There is no evidence to indicate that the anomaly is exclusively or even partially caused by velocity structure. A region of high attenuation could equally well be responsible for the phenomenon. Further there is no evidence from these data that unequivocally puts the anomaly at the base of the mantle. It is attractive to do so in that the anomalous region could be sited under Hawaii and have a radius of about 200 km, but nothing positively requires the anomaly to be so placed.

Davies and Sheppard¹⁰ showed that the direction of approach of P-waves from the South Pacific at LASA showed rapid fluctuations with azimuth and it is of interest to correlate these with these amplitude data. The transition from mainly distance-mislocations to combinations of azimuthal and distance terms on an azimuth of 265° in Fig. 5 of ref. 10 seems to occur at about the same place (11° S, 165° E) that amplitudes change rapidly. The fact that amplitudes are severely diminished from the New Hebrides region reduces the number of events for which location anomalies can be plotted in this region so the transition to the Fiji-Kermadec region is less clear; further it seems that there is substantial complexity in the latter region which will not be discussed here. The only remark that we can make with any confidence is that it is clear that the amplitude anomaly, whilst being reflected somewhat in directional anomalies, is not symmetrical in its effect on direction of approach.

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R. E. NEEDHAM
D. DAVIES

Lincoln Laboratory,
Massachusetts Institute of Technology,
Lexington, Massachusetts 02173

Received May 9, 1973.

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Quasi-monochromatic 0.05 Hz Waves in Cape Waters

REGULAR monitoring of ocean gravity waves just north of Cape Town reveals the predominant frequency range as 0.07–0.10 Hz. These waves generally exhibit narrow swell type energy spectra but nonetheless have a small range of frequencies present. The case history described here is interesting because of the low frequency (0.05 Hz) and because it is monochromatic.

On June 26, 1972, a record of a remarkably regular 0.05 Hz swell of height about 1 m was registered by a Wemelsfelder wave recorder situated on a tower in 13 m of water 15 miles north of Cape Town, South Africa. Figure 1a is a sample from the 30 min recording, at 1200 h. Figures 1b and c are respectively the autocovariance curve (which is only slowly damped) and the spectrum (which is sharply peaked).

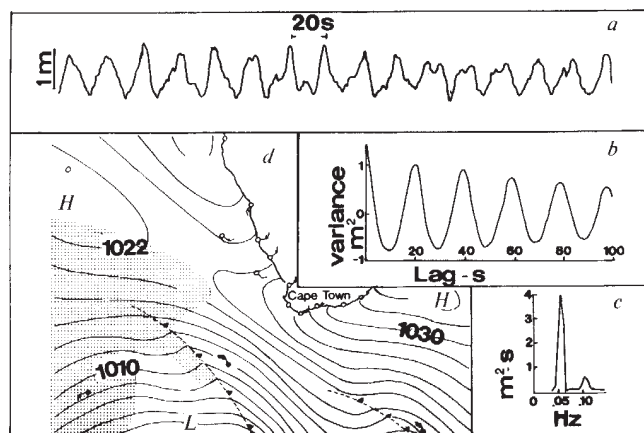


Fig. 1 a, Tracing of wave record, b, autocovariance curve; c, spectrum of record, digitized at intervals of 1 s; d, synoptic chart for 1400 h on June 26, 1972.

Consideration of energy distribution in frequency-time space suggests the swell originated some 1,000 nautical miles away. Figure 1d is the relevant part of the synoptic weather chart published by the South African Weather Bureau for 1400 h on June 26, 1972. On it the area from which waves could be generated towards Cape Town has been shaded. (It was assumed that waves are generated $\pm 20^\circ$ to the wind direction.) The deduced geostrophic wind velocities in the shaded area are rather lower than are usually associated with 0.05 Hz waves¹, though they may be in error. The isobars are notably straight and slope from north of west as they did in the previous and following days. In our experience this is not a common condition. The front shown on the synoptic chart passed over Cape Town on the afternoon of June 27, 1972. Presumably the surf swell was the forerunner of this front.

The interception of the swell was made possible by frequent monitoring (every 2 h) of the sea state. The monochromatic nature of the record is in part due to the unusually low level of background noise. The arrival of the swell increased the variance by an order of magnitude.

T. F. W. HARRIS
J. N. MARSHALL
F. A. SHILLINGTON

Department of Oceanography,
University of Cape Town

Received March 12, 1973.

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C₁₈-Isoprenoid Ketone in Recent Marine Sediment

ISOPRENOID hydrocarbons, fatty acids and alcohols occur in ancient rocks, oil shales, young sediments and living organisms^{1,2}. During thermal alteration experiments on a recent marine sediment from Tanner Basin, Southern California continental shelf, we isolated a C₁₈-isoprenoid ketone, namely 6,10,14-trimethylpentadecan-2-one. Samples of sediment from the Tanner Basin were sealed in glass bombs and exposed to temperatures from 60° to 150° C for 7 d, 30 d and 60 d. The sediment was then extracted with benzene-methanol and the extract chromatographed on a silicic acid column. The ketone was found in both the heat-treated and untreated sediment. It was extracted with the fatty acid fraction which had been converted to methyl esters, and was separated with the other branched components by the urea adduction method. For comparative purposes, the C₁₈-isoprenoid ketone was also synthesized³. Analytical comparisons by gas-liquid chromatography, using two 5 foot $\times \frac{1}{8}$ inch columns (3% OV 101 on 100/120 mesh 'Gas Chrom' Q and 3% DEGS on 100/120 mesh 'Gas Chrom' Z), showed the synthetic product to be identical to the sedimental ketone.

We obtained a mass spectrum of the ketone using a gas chromatograph coupled with a CEC-21-491 mass spectrometer. The spectrum showed a molecular ion peak at m/e 268 with fragmentation peaks at m/e 250 (M-18); 235 (M-33); 225 (M-43) and 210 (M-58). Loss of $[\text{CH}_3\text{-CO}]^+$ and $[\text{CH}_3\text{-CO-CH}_2]^+$ gave abundant fragments at m/e 43 and 58, respectively (Fig. 1). This pattern is compatible with synthetic C₁₈-isoprenoid ketone reported by Cox *et al.*⁴. Further evidence for ketone structure was also gained from infrared spectroscopic measurements. A weak absorption band (due to small sample size) was observed at $1,714\text{ cm}^{-1}$ (in CCl_4), which is characteristic of a saturated methyl ketone. The NMR spectrum (in CCl_4) showed the expected signals for CH_3CO protons (δ 2.03 p.p.m.), CH_2 protons adjacent to the CH_3CO group (triplet δ 2.25, 2.3, 2.35 p.p.m.), other CH_2 protons as well as CH protons (multiplet centred at δ 1.25 p.p.m.) and $(\text{CH}_3)_2\text{CH}$ protons (δ 0.82 and 0.9 p.p.m.). The identity of the ketone was further substantiated by *in situ* formation of a yellow 2,4-dinitrophenylhydrazone on thin-layer plates (silica gel GF-254). The measured R_F of 0.66 (triple developed with chloroform-hexane, 3:1) was the same as for the synthetic ketone.

The data (Table 1) show the influence of temperature and time of heating upon ketone generation. The ketone

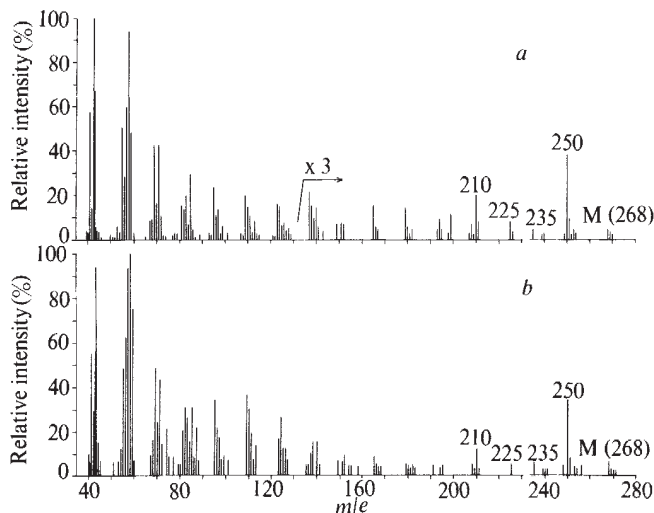


Fig. 1 Mass spectra of, a, synthetic C₁₈-isoprenoid ketone; b, ketone isolated from sediment.

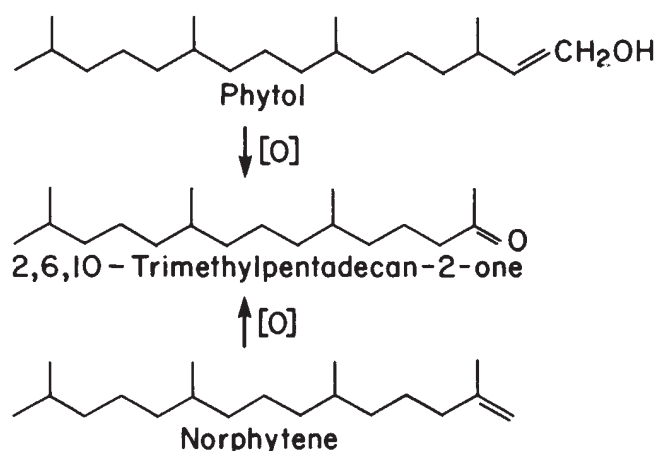


Fig. 2 Possible formation of isoprenoid ketone.

was present initially in the sediment at the concentration of 0.160 p.p.m. The maximum yield was obtained by heating the sample at 150° C for one month. Comparing the quantity of ketone formed from natural and freeze dried samples (150° C, 2 months) indicates considerable inhibition of ketone accumulation in the freeze dried sample.

Table 1 Concentration of C₁₈-Isoprenoid Ketone in Tanner Basin Heat-treated Sediment (Parts per Thousand Million)*

Time (d)	65	Temperature (°C)	100	150
7	140	880	1,240	
30	500	1,440	4,700	
64	50	730	2,100	
64	—	—	820†	

* Determined by gas chromatography. Accuracy of total extraction procedure estimated to be ±0.05 p.p.m.

† Freeze dried before heating.

Although other contributors, such as vitamin K₁, α-tocopherol and phospholipids from halophilic bacteria^{5,6} and algae⁷ which have been shown to possess a phytol side chain, are also possible, the most obvious source for the ketone is phytol, originally derived from chlorophyll. A detailed consideration of the processes leading from phytol to the ketone is premature, but various pathways may be invoked to account for the formation of the ketone (Fig. 2). One is the oxidative degradation of norphytene, which was isolated from various plankton, fish and mammalian oils⁸, and probably originates from phytol concentrated by zooplankton, followed by dehydration under acid catalysis of the digestive tract of marine animals. The C₁₈-ketone could also be formed during diagenesis, by oxidation of the allylic alcohol phytol, possibly biologically catalysed, during the early stages of sedimentation. We favour the occurrence of the second pathway during heating⁴.

R. IKAN*
M. J. BAEDECKER
I. R. KAPLAN

*Institute of Geophysics and Planetary Physics,
University of California,
Los Angeles, California 90024*

Received April 2, 1973.

* Permanent address: Department of Organic Chemistry, Natural Products Laboratory, Hebrew University, Jerusalem.

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Calcium Concentration in the Shell of the Bivalve *Chione undatella* Sowerby

GROWTH ring patterns in bivalves are associated with ontogenetic and environmental changes; as growth rate declines with age, growth increments narrow, and as the seasons shift, growth rings vary in width¹. Although for some purposes calcium concentration has been assumed to be uniform throughout the shell², the concentration is known to vary³; it seems that examination of increases and decreases in calcium concentration would yield information about metabolic fluctuations similar to the ontogenetic and environmental information revealed by growth ring patterns. Such information obtained from fossils could then enable investigation of fossil metabolism, or description of changes in calcium distribution with

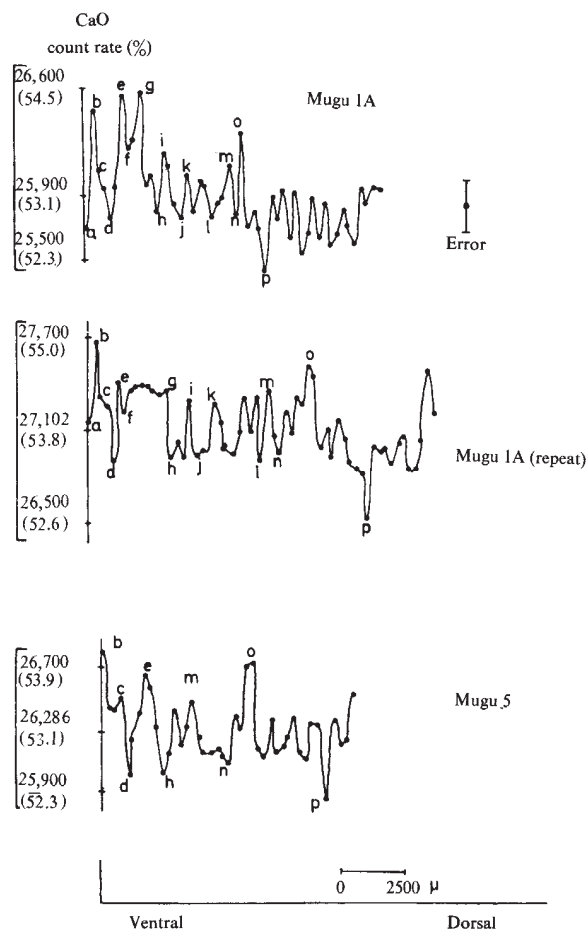


Fig. 1 Calcium distribution along the median ventral-dorsal axis of two specimens of sectioned *Chione undatella*. Measurements taken at the ventral margin of the shell are plotted at the left end of the abscissa, points graphed farther to the right are successively more dorsal. Calcium abundance is given on the ordinate as count rate per 10 s (approximate range in concentration and sample mean for each traverse) and as % CaO in pure CaCO₃. Letters designate oscillations which repeat from shell to shell.

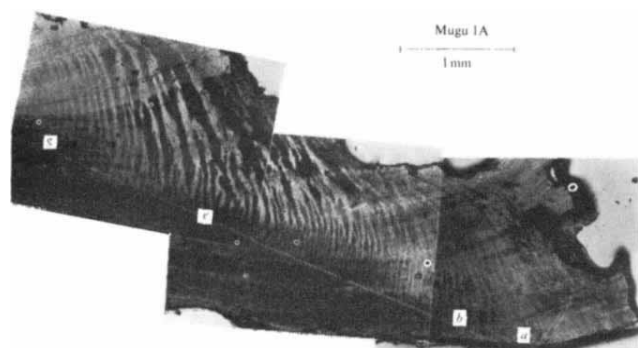


Fig. 2 Composite acetate peels of ventralmost section of specimen Mugu 1A to show correspondence between microprobe measurements and shell growth pattern. Letters correspond to those of Fig. 1.

diagenesis of fossils. Cycles of calcium concentration in fossil shells may, like growth ring patterns^{4,5} at the structural level, provide chemical data pertaining to variation in the rate of the Earth's rotation through time.

Analyses of the variability of calcium content in shells have been made possible by the successful application of electron microprobe techniques to the study of invertebrate skeletons⁶⁻⁸. An electron microprobe was used in this study to measure changes in the abundance of calcium along the median, ventral-dorsal axis of sectioned shells of the bivalve *Chione undatella* Sowerby. Standard preparation techniques were used. Sixteen live adults were removed from Mugu Lagoon, near Oxnard, California, on April 30, 1970, and were analysed for calcium distribution along the ventralmost 2 cm of each specimen. The analyses of each specimen were repeated at least twice and totalled forty-four. The microprobe was operated at 15 kV with a sample current of 0.02 μ A and an electron beam with a large diameter (25 μ m) to prevent destruction of the specimens. A piece of homogeneous calcite was used as a standard enabling drift corrections. A calcium count rate averaging 27,000 counts per 10 s and a variability of less than 1,500 counts per 10 s made background and dead-time corrections unnecessary. Calcium concentration was estimated from count rate by the method of first approximations.

The error of each calcium measurement is $\pm\sqrt{n}$ where n is the count rate for that measurement (Fig. 1). The variability of the measurements about the respective traverse mean is given as $\pm 3\sqrt{N}$ where N is the traverse mean. The graphs thus show the data are close to limits of random X-ray variation. The recurrence of similar patterns of calcium distribution in repeated traverses is, I believe, evidence of actual, regular calcium variation lying close to the limits of random X-ray variation.

In thirty of the analyses, the average calcium content increased a maximum of 2% ventrally (Fig. 1). In four analyses (all of the same shell), the content decreased ventrally. In the remaining ten analyses the average calcium concentration was uniform along the traverse. In all cases the range between the maximum and minimum concentration was less than 3%.

Repeated traverses of each shell enabled discrimination between regular oscillations of calcium concentration and patterns produced by random X-ray variation. Such differentiation is not clear in all cases; patterns are never quite identical due to variations in the number and location of points on each traverse. Consequently, areas of divergent concentration may not appear at the same place on the different graphs of each specimen.

In spite of this difficulty, it is possible to recognize regular oscillations of calcium concentration and to correlate the patterns from shell to shell (Fig. 1). Patterns were matched beginning with recently deposited calcium along the ventral margin. Correlation was aided by the observation that con-

secutive points of relatively high calcium abundance (points *b* and *e-g*) coincided with narrow bands of poorly defined growth rings representing (postulated) winter growth (Fig. 2). The oscillations may thus be synchronous with environmental changes. The lettered points on the graphs of samples Mugu 1A and Mugu 5 form a pattern which is repeated in two additional specimens.

There are alternative explanations for the variations in calcium concentration. Calcium concentration may be inversely correlated with carbon concentration. Carbon abundance was measured simultaneously with calcium, and although the limits of microprobe accuracy require cautious interpretation of carbon analyses, carbon concentration did appear inversely proportional to calcium abundance in a few cases. On the other hand, fluctuations in trace element abundance or changes in shell porosity or mineralogy may influence calcium concentration.

Additional data are needed to determine the significance of the variable calcium distribution in the shell of *Chione undatella*. The many metabolic and environmental factors influencing growth and calcification have been summarized⁹⁻¹¹ and it is known that the cause and effect relationships between environment and shell secretion are complex. If such relationships can be resolved, it may eventually be possible to study calcium metabolism in living and fossil bivalves by analysing distribution of calcium in the organisms' shells.

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GARY D. ROSENBERG

Geology Department,
UCLA,
Los Angeles, California 90024

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BIOLOGICAL SCIENCES

Reflex Balance

THE notion of "balance" ordinarily implies some underlying insecurity or liability to loss of equilibrium. Thus a pencil set up on its butt end may be technically in stable equilibrium, yet, because the centre of gravity lies some way above the relatively small area of support, we speak of the condition as one of "precarious balance". The situation of a man standing erect is somewhat similar, though here the posture is maintained by muscular activity which is reflexly adjusted to counter the effects of forces that might disturb the equilibrium. These adjustments are usually so successful, and falling is consequently so unusual, that we tend to forget the inherent insecurity of the posture.

Success in the maintenance of the upright posture is usually attributed to reflexes initiated from receptors in the labyrinth

of the inner ear. Traditional accounts of the working of these reflexes, however, fail to account for the observed stability. According to Magnus¹, a change in the position of the head alters the extensor tone in all four limbs of an animal in symmetrical fashion. But symmetrical forces are not appropriate here. What is needed is the development of forces directed to oppose the threat to equilibrium and to resist displacement.

I have accordingly re-examined the reflex effects upon the limbs that can be elicited by tilting the head. I have used cats decerebrated at a level slightly in front of the usual intercollicular plane to avoid excess rigidity of the limbs. I have been able to separate the responses in the labyrinth reflexes from those in the neck reflexes by the following procedure.

The first two cervical nerves are cut on each side within the spinal canal to interrupt the signals from the receptors in the intervertebral joints. The trunk, the axis vertebra, and the skull of the animal are mounted on separate supports. The head can now be tilted while the axis vertebra is held stationary in its clamp. Neck movements occurring between skull and axis vertebra generate no neck reflexes in these conditions because the relevant joints are denervated. The responses seen are thus labyrinth reflexes without neck reflexes. Alternatively, the axis vertebra may be rotated to twist the neck while the head remains stationary in its clamp. This produces neck reflexes without labyrinth reflexes because the innervation of the lower intervertebral joints is still intact. Although the intensity of the responses is reduced by the partial denervation, there is no ambiguity about the direction of the changes in the limbs.

The labyrinth reflex responses to head tilting have been found to be invariably asymmetrical and appropriate to a stabilizing function, in contrast to the symmetrical scheme put forward by Magnus. The effects of fore-and-aft head tilting on extensors of the hind limb were reported in 1963 (ref. 2), effects on the forelimb in 1967 (ref. 3), of lateral head tilting on both forelimb and hind limb in 1970 (ref. 4), and the opposing effects of labyrinth and neck reflexes upon a single extensor muscle of the forelimb in 1972 (ref. 5). The responses in the labyrinth reflexes may be summarized in the phrase: "downhill limbs extend", with the implication of flexion in the corresponding "uphill" limbs.

When the neck is twisted by rotating the axis vertebra towards right side up, the stimulus to the neck reflexes is the same as would be produced by a head rotation that carries the chin towards the right side. The response in such an experiment consists of extension of both limbs on the right side, fore and hind, with flexion on the left, that is, "chin limbs extend" in agreement with the scheme for neck reflexes set out by Magnus and de Kleijn¹.

It should be emphasized that the responses in the neck reflexes are in the opposite sense to the responses in the labyrinth reflexes for the same tilt of the head.

Where both sets of reflexes are available their effects may be in conflict. A head tilt towards right side up should by stimulating the labyrinth produce extension of the limbs of the left (downhill) side with flexion on the right, while the concomitant neck torsion should produce extension on the right side (chin limbs) with flexion on the left. A corresponding conflict arises for head tilts in either direction about any horizontal axis. One may argue that, if the conflicting reflex drives are equally potent, and if the conflict is resolved centrally, one should expect no change in limb tone when the head is tilted in any direction without moving the trunk. This is in fact what happens (though the possibility of some other explanation is not excluded). It follows that the reflex effects on the limbs do not serve to stabilize the head. Can one say anything useful about their effects on the trunk?

If the trunk is to be tilted as well as the head, the interaction of neck and labyrinth reflexes becomes a little awkward to visualize. To simplify matters I have constructed a model in which the effects of the two sets of reflexes upon the limbs are

simulated by mechanical linkages so adjusted as to make the neck and labyrinth "reflexes" equally potent in their effects on the limbs.

In the model, head movement without trunk movement naturally produces no change in the limbs because the effects of the two sets of linkages have been adjusted to cancel out. What was unexpected, however, is that the interaction of the two sets of reflexes appears to have the effect of stabilizing the trunk, even though the trunk contains no detector of the direction about which the stabilization is to be effected. The effect of the interaction between neck and labyrinth reflexes is to transfer the stabilizing influence of the detector from the head to the trunk; and the limb posture is such as to keep the trunk from being overturned when the supporting surface is tilted, or when the animal stands on uneven ground.

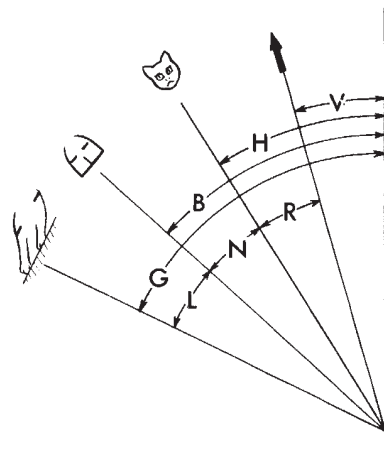


Fig. 1 Nomenclature of angles of tilt in roll, taken as positive towards right side down.

The nature of the interactions can be indicated by the following algebraic scheme. This is intended merely as a shorthand qualitative description to help in predicting the direction of the overall responses, without prejudice as to the nature of such mechanisms as may be envisaged as carrying out the necessary arithmetical computations within the animal's nervous system.

We consider tilts about a particular horizontal axis, say, the fore-and-aft (roll) axis, with the notation of Fig. 1. The support vector in this diagram is the resultant of all the contact forces acting on the skull. When the animal is at rest on the Earth's surface, this vector is that representing the force preventing the skull from accelerating toward the centre of the Earth under the action of gravity. (Note that a particular magnitude and direction of resultant contact force applied to the skull, such as, for example, $0.7g$ from left to right along the bimodal axis, will produce the same deformation of the otolith apparatus no matter how the direction of this axis is oriented in relation to the gravitational field. Because it accelerates the denser and the less dense parts equally, the force of gravity cannot, of itself, contribute any relative deformation of the otolith apparatus that could excite the receptors.)

The direction of the support vector is denoted as V , measured from some reference direction, such as a radius of the Earth.

The stimulus to the otolith organs in the positional reflexes is H minus V , which we denote as R (for "roll" in this case); the stimulus to the neck reflexes is H minus B , denoted as N ; and the response in the limbs is measured as the angle of asymmetry, G minus B , denoted as L .

The effect of the labyrinth reflex upon the limbs is expressed as "downhill limbs extend", or $L_1 = k_1 R$. The effect of the neck reflexes, "chin limbs extend", is $L_2 = -k_2 N$. The combined effect of the two sets of reflexes may be supposed to correspond to the relation $L = L_1 + L_2 = k_1 R - k_2 N$.

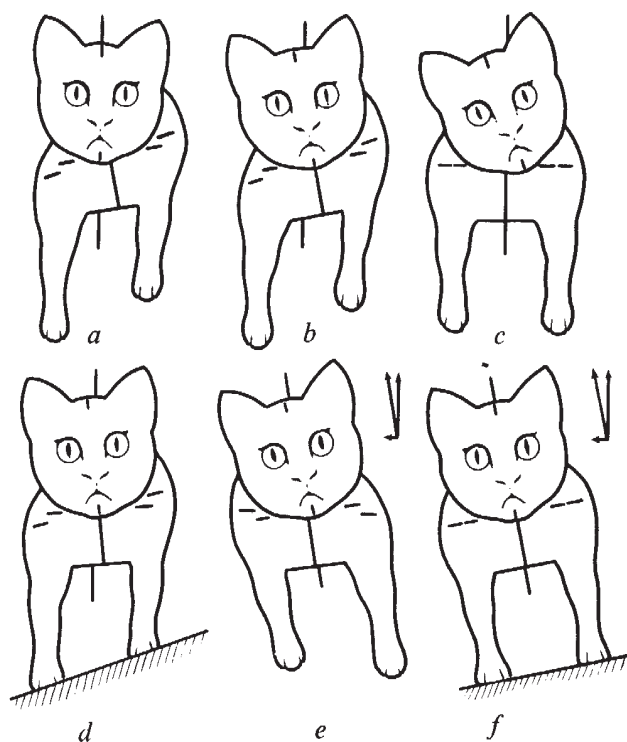


Fig. 2 *a*, Neck reflexes alone. Body tilted, head erect. Chin limbs extend. Figs 2*a-f* are from photographs of a model in which the limb movements are driven from the head movements by the interaction of two sets of mechanical linkages that simulate respectively the effects of neck reflexes and of labyrinth reflexes. The relative extension of the limbs can be gauged by the displacement of the markers at the shoulder. *b*, Labyrinth reflex alone. Body and head both tilted, neck straight: downhill limbs extend. *c*, Head tilt alone. Head tilted, body erect. Limbs symmetrical. *d*, Uneven ground. Body tilted, limbs in compensatory pose, head free to take up any position. *e*, Lateral acceleration constant. Limb asymmetry corresponds to tilt of body relative to support vector. *f*, Lateral acceleration constant. Limbs symmetrical on suitably inclined support.

Case A: neck reflex alone (Fig. 2*a*):

$$V=0, H=0, B=\beta \\ L=k_1R-k_2N=k_2\beta, \text{ the limbs of the right side extend.}$$

Case B: labyrinth reflex alone (Fig. 2*b*):

$$V=0, H=\alpha, B=\alpha \\ L=k_1R-k_2N=k_1\alpha, \text{ the limbs of the right side extend.}$$

Case C: head tilt alone, that is, head tilted, body upright (Fig. 2*c*):

$$V=0, H=\alpha, B=0 \\ L=k_1R-k_2N=\alpha(k_1-k_2). \text{ This means that, if no limb movement occurs, as is usually the case, } k_1 \text{ must be equal to } k_2.$$

Case D: uneven ground (Fig. 2*d*):

$$G=\gamma, V=0, H=\alpha, B=\beta \\ L=k_1R-k_2N=k_1\alpha-k_2(\alpha-\beta)=k\beta, \text{ if } k_1=k_2=k, \text{ and } \\ G=\gamma=L+B=\beta(1+k), \text{ or } \beta=\gamma/(1+k), \text{ which is independent of } \alpha, \text{ so that the head may take up any position, free from reflex restraint.}$$

Case E: lateral acceleration constant (Fig. 2*e*):

$$V=\phi, H=\alpha, B=\beta \\ L=k(\alpha-\phi)-k(\alpha-\beta)=k(\beta-\phi), \\ \text{and } G=L+B=\beta+k(\beta-\phi).$$

This means that the limb posture corresponds to the compensatory pose appropriate to an inclined support, and that the head may still take up any position.

For β to be equal to ϕ , G must also be equal to ϕ , so that the body and limbs are symmetrically disposed on a support surface normal to the direction of the support vector (Fig. 2*f*). This is what happens in an aircraft executing a correctly banked turn.

Case F: Lateral acceleration not constant. A change in the magnitude of the lateral acceleration implies a rotation of the support vector. The dynamic component in the response of the receptors in the labyrinth has the effect of moving the body until its plane of symmetry corresponds with the new direction of the support vector. If the head were to move through a corresponding angle, however, this would involve angular accelerations of the skull and would bring into play the acceleratory reflexes from the semicircular canals. These acceleratory reflexes generate forces in the neck muscles and in the limbs in such a direction as to oppose the angular acceleration of the skull. The effect is as though the moment of inertia of the skull has been increased, so that it tends to stay behind. This leads to a temporary loss of balance during changing lateral acceleration, as occurs when a man stands on a platform that suddenly begins to move. The acceleratory reflexes normally act only so long as the direction of the support vector is actually changing. When the forces become steady, the stabilizing reflexes take over again.

The new scheme can be generalized to tilts about any horizontal axis—lateral, fore-and-aft, or diagonal—and to any field of accelerations.

An important consequence of the way the reflexes from neck and labyrinth interact is that effective stabilizing action of the limbs is applied to the trunk in a pattern such as might have been generated by a directional sensor located in the trunk, and this in spite of the fact that we know that the relevant sensor lies in the skull and not in the trunk. Furthermore, the skull can be inclined in any direction without altering the pattern of trunk stabilization, even though such tilting must necessarily affect the directional sensor contained in the skull.

T. D. M. ROBERTS

*Institute of Physiology,
University of Glasgow*

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Evolutionary Relationship between Carboxyterminal Region of a Human Alpha Chain and Other Immunoglobulin Heavy Chain Constant Regions

FROM an evolutionary point of view the earliest immunoglobulins to appear are widely considered to be members of the IgM class, primarily because of their presence in many lower phylogenetic forms¹. The IgG class is believed to be of more recent origin. In spite of their biological importance, comparatively little is known of the evolutionary history of IgA molecules as alpha chain amino acid sequence determinations have been limited to small portions of the hinge region^{2,3}, certain cystine peptides⁴ and the carboxyterminal octapeptide⁵. Most authors have assumed that IgA diverged from the other classes more recently than did IgG because IgA was difficult

to identify in birds, and has not been found in reptiles, amphibians or lower vertebrates. We report here amino acid sequence data on a human alpha chain which imply a close evolutionary relationship between alpha and mu chains.

A 500 mg sample of a human alpha chain (from the IgA1 protein Zap) was digested with cyanogen bromide⁶ and chromatographed on 'Sephadex' G25 in 1.0 M propionic acid. One peak appeared in the void volume, and a second exited near the total volume of the column. This second fraction, which contained neither homoserine nor homoserine lactone, was termed H-4 and corresponded to the carboxyterminal cyanogen bromide fragment sequenced by Prahl *et al.*⁵. The void volume fraction was lyophilized and repassed on a 'Sephadex' G100 column in 5.0 M guanidine-HCl. Two peaks were again detected. The first peak gave two sequences in the automated sequencer, one of which was the amino terminal sequence previously determined on the intact heavy chain. The second sequence was homologous with that section of the V_HIII subgroup of immunoglobulin heavy chains which starts at position 86⁷. To obtain these fragments in purified form the first peak was totally reduced in a denaturing buffer and repassed on the same column of 'Sephadex' G100. As amino acid analysis of fully oxidized⁸ intact Zap heavy chains showed that this alpha chain contained three methionine residues, and as the amino terminal fragment was linked by an intrachain disulphide bond to the fragment which begins at residue 86 (the 22-98 disulphide bond characteristic of V_HIII proteins)⁷, the 31-residue piece isolated from the second peak of the initial passage through 'Sephadex' G100 (termed H-3) must be the penultimate cyanogen bromide fragment of this heavy chain.

Most of the sequence of H-3 was determined on an updated Beckman model 890A sequencer with a peptide program, utilizing an undercut cup and a nitrogen flush developed in collaboration with Dr Jack Ohms of Beckman Instruments, Palo Alto, California. As Fig. 1 shows, twenty-nine of the thirty-one residues were identified by direct sequencer analysis. The last three residues were determined by carboxypeptidase digestion, to provide a one residue overlap. After trypsin digestion, three peptides were isolated on a 'Dowex' 50X4 column using a pyridine-formic acid buffer system⁹. The summed compositions of the three tryptic peptides accounted for all the residues included in the established sequence. In addition, peptide T-3 (Fig. 1) was subjected to direct sequencer analysis as well as carboxypeptidase digestion to confirm some of the residues in the carboxyterminal region of H-3.

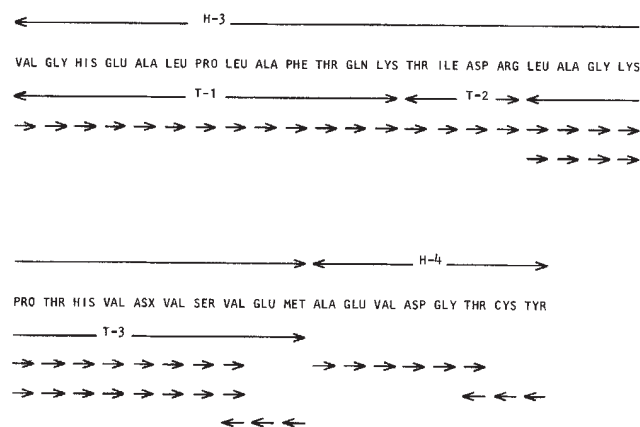


Fig. 1 Amino acid sequence of the carboxyterminal region of the human alpha-1 chain Zap. The penultimate cyanogen bromide fragment is labelled H-3, and the carboxyterminal octapeptide is labelled H-4. Arrows to the right indicate successive automated Edman degradations and arrows to the left indicate identification with carboxypeptidase A. The three tryptic peptides derived from H-3 are labelled T-1, T-2 and T-3. Only T-3 was subjected to automated sequencing.

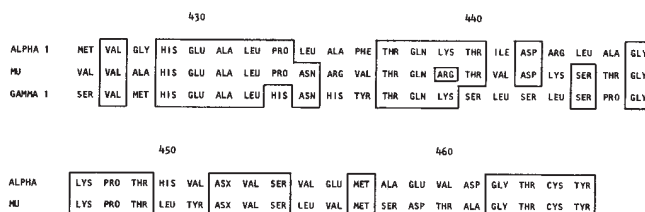


Fig. 2 Comparison of the carboxyterminal regions of human immunoglobulin heavy chain constant regions.

The first six residues of the octapeptide (H-4) were also identified by sequencer analysis. Carboxypeptidase digestion established the three carboxyterminal residues. As noted by others⁵, the carboxyterminal tyrosine was obtained in a yield of only 0.4 mol per mol of peptide.

The lysine-proline bond at positions 447-448 (Fig. 1) was evidently resistant to tryptic hydrolysis as peptide T-3 was recovered intact. No other tryptic peptides obtained could correspond to sections 444-447 or 448-457. Such resistance of lysine-proline bonds to tryptic digestion is well known¹⁰.

Sequence relationships of the carboxyterminal regions of human immunoglobulin heavy chains are shown in Fig. 2. The numbering is from the presumed residue 426 of the alpha chain, based on homology with the human IgG1 protein Eu¹¹. The closeness of the alpha and mu chains is particularly striking, with twenty-two of the forty residues compared being identical (55%). This homology is considerably greater than that yet found by any other interclass constant region comparisons. Of the eighteen positions in which mu and alpha chains differ, fourteen can be accounted for by a one base change in the genetic code, and four by two base changes. It is also significant that the alpha and mu chains extend exactly the same distance beyond the carboxyterminal residue of the gamma chain (Fig. 2).

These sequence patterns suggest a closer evolutionary relationship between mu and gamma than between alpha and gamma chains. The extension of the alpha and mu chains nineteen residues beyond the termination of the gamma chain allows comparison of only twenty-one positions for all three heavy chain constant regions. In this common stretch, all three chains share an amino acid in eight positions and the alpha and mu chains are the same in eleven.

On the basis of comparisons of amino acid sequences, several authors have proposed that the immunoglobulin variable and constant regions diverged about 400 million years ago, approximately when vertebrates appeared¹². Recent data on the amino acid sequence of the human mu chain¹³ would indicate that gamma diverged from mu about 300 m.y. ago. A comparison of human IgG1 and IgG4 subclass sequences has led to the proposal that the human IgG subclasses diverged about 25 m.y. ago¹⁴. Although the calculation of the rate of evolutionary divergence of proteins on the basis of the frequency of amino acid interchanges requires numerous assumptions, the rate seems to be roughly constant for a given protein type¹⁴. Excluding the "hinge" region of immunoglobulins from these calculations, most authors have assumed that, for these molecules, one difference per 100 residues became incorporated about every 4×10^8 to 5×10^8 yr¹²⁻¹⁴. It has also become clear that, among the immunoglobulins, a stretch of forty residues (excluding the "hinge" region again) is generally sufficient to ascertain the degree of relatedness of an entire chain.

The data presented here suggest that the alpha chain diverged from the mu chain about 200 m.y. ago. This would place the divergence of the IgA molecule very early in mammalian evolution as mammals are believed to have appeared about 175 m.y. ago¹⁵. As birds diverged at about the same time, but from a different branch of reptiles, it has been difficult to predict, on an evolutionary basis, whether or not modern birds should have IgA. Recent studies in several laboratories, however, suggest that there is an avian counterpart to human IgA¹⁶⁻¹⁸. On the

basis of the scheme suggested here for the divergence of IgM and IgA, it seems unlikely that modern reptiles, amphibians or fish will be found to possess IgA because the class would have had to arise independently in each of these distinct groups of animals.

The proposed divergence of IgA from IgM is complicated by the apparent presence in IgM of an additional "homology" region. If, as suggested here, IgA diverged from IgM approximately 100 m.y. after IgG diverged from IgM, one would have to assume that both IgA and IgG independently deleted a "homology" region, since the alpha-1 chain is clearly closer in overall length to the gamma than to the mu chain. However, the recent observation that the IgG3 heavy chain contains an additional section of 8,000 molecular weight¹⁹, the accumulating evidence that the hinge portion of immunoglobulin heavy chains may be encoded by a separate gene^{20,21}, and the demonstration of a difference of 5,000 between the molecular weight of the human IgA subclasses themselves²², complicates evolutionary arguments based only on immunoglobulin heavy chain size.

Alpha and mu chains share several structural and functional features. Both contain relatively large amounts of carbohydrate as compared with IgG²³, both have a strong tendency to polymerize, and both contain an additional polypeptide termed the "J" chain when in the polymerized form^{24,25}. Also, IgA and IgM proteins both have a strong tendency to bind certain other serum proteins such as albumin²⁶. Finally, in certain human patients who lack the capacity for IgA formation, IgM replaces IgA in secretions²⁷. The sequence data reported here suggest that the functional relatedness characteristic of the two classes may have its origin in their close evolutionary history.

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CHE-YEN CHUANG
J. DONALD CAPRA
J. MICHAEL KEHOE

Department of Microbiology,
Mount Sinai School of Medicine of
the City University of New York,
10 East 102nd Street,
New York, New York 10029

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Effects of Antibodies to Luteinizing Hormone-Releasing Hormone in the Male Rabbit and on the Rat Oestrous Cycle

PITUITARY gonadotrophin secretion is stimulated by luteinizing hormone-releasing hormone (LH-RH) from hypothalamic extracts¹. The synthetic compound has similar effects, releasing luteinizing hormone and follicle stimulating hormone in rats^{2,3} and humans⁴. Selective neutralization of this releasing hormone, for example, by a specific antibody, would be important in the study of its action. Although this method has been used to neutralize other hormones⁵, they were acting through the systemic circulation, unlike the releasing hormones which act via the localized hypothalamic-pituitary portal system.

Five rabbits, three male and two female, were immunized with synthetic LH-RH conjugated to bovine serum albumin (BSA) using the carbodiimide technique as previously described⁶. At the time of injection the three male animals had testes of normal size. Eight weeks later, when receiving booster injections, their testes had decreased slightly in size. The rabbits were kept alive for a further two months, and their gonads and other endocrine glands were examined at autopsy. Testicular atrophy was obvious in the three male animals. To elucidate the changes which had occurred, testes were examined from rabbits which had been immunized at the same time with thyrotrophin releasing hormone (TRH) conjugated to BSA. Both antibody producers and non-producers were studied. The testes of the LH-RH immunized animals were found to weigh between 350 and 400 mg, 15% of the controls.

Histological sections of different areas of the testes were prepared. In the control animals, spermatogenesis was seen to be progressing normally, but in the three male rabbits producing antibody to LH-RH there was marked involution of the seminiferous tubules. These were lined by a single layer of cells and there was no evidence of spermatogenesis (Fig. 1). Female rabbits have been kept alive as a source of antibody so that no information is yet available on the state of their gonads.

The presence of antibody to LH-RH was assessed by testing serum from the immunized animals for its capacity to bind radioiodinated LH-RH. Techniques of radioiodination and the *in vitro* properties of the antisera relating to the establishment of radioimmunoassay of LH-RH have been described elsewhere^{6,7}. The animals were found to have produced antibody which had inactivated endogenous

LH-RH and had consequently reduced pituitary gonadotrophin secretion.

To study whether the antisera could neutralize LH-RH when passively transferred, the effect of the antisera on the rat oestrous cycle was examined. Normal adult female Sprague-Dawley rats were maintained in an air-conditioned room illuminated between 0500 h and 1900 h. Only rats which had exhibited at least two consecutive four-day cycles were used. These were injected intravenously with 1.0 ml antiserum, under ether anaesthesia, at different stages of the cycle, controls being injected with 1.0 ml normal rabbit serum (NRS).

Table 1 Effects of Neutralization of LH-RH at Various Times on Dioestrus 1 and Dioestrus 2

Treatment	Pro-oestrus vaginal smears/total	Rats with uterine distension/total
NRS D1	7/7	7/7
Antiserum D1	2/11	0/11
Antiserum D2	4/4	3/4

Rats autopsied on afternoon of expected pro-oestrus.

Eleven rats received antiserum on the first day of dioestrus (D1) and were autopsied on the afternoon of expected pro-oestrus. None of them exhibited uterine distension and nine had vaginal smears typical of the second day of dioestrus (D2). Controls injected with NRS behaved normally (Table 1). Antiserum was not effective in preventing pro-oestrus in animals injected on the second day of dioestrus (Table 1). Our results indicate that LH-RH is necessary for the events leading to the pro-oestrus state before the second day of dioestrus.

To study the involvement of LH-RH on the established "critical period" of hormonal events occurring in the afternoon of pro-oestrus and leading to ovulation⁸, antiserum was

administered to rats between 1200 and 1600 h, controls receiving NRS. On the morning of the day of normal oestrus, animals were autopsied and the presence of ova determined by examination of the oviducts under the dissecting microscope. All rats injected with antiserum before 1430 h on the day of pro-oestrus had failed to ovulate and demonstrated uterine distension. Controls did ovulate and the expected loss of intrauterine fluid had occurred (Table 2). These results present the most direct evidence to date that LH-RH is essential for the hormonal stimulus leading to ovulation in the rat.

Table 2 Effects of Neutralization of LH-RH at Various Times on the Day of Pro-oestrus

Treatment	Rats ovulated/total	Rats with uterine distension/total
NRS 1200	5/5	0/5
Antiserum 1200	0/5	5/5
Antiserum 1400	0/5	3/5
Antiserum 1430	0/8	8/8
NRS 1400	6/6	1/6
Antiserum 1500	2/4	2/4
Antiserum 1600	2/2	0/2

Rats autopsied on morning of expected oestrus.

Studies are in progress to elucidate the detailed hormonal changes effected by neutralization of LH-RH. With available antisera, LH-RH can be detected at concentrations of less than 20 pg *in vitro* which makes possible radioimmunoassay of LH-RH in laboratory animals and in man^{6,9}.

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HAMISH M. FRASER
ANDREW GUNN

Department of Surgery,
The University, Dundee

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Identification by Radioimmunoassay of the Luteinizing Hormone-Releasing Hormone in Human Urine

LUTEINIZING hormone-releasing hormone (LH-RH) is a decapeptide that has been identified in the hypothalamus of several species. Both the natural and synthetic peptides are active in stimulating the release of pituitary LH and follicle stimulating hormone (FSH) in many species including man¹. We have developed a radioimmunoassay for

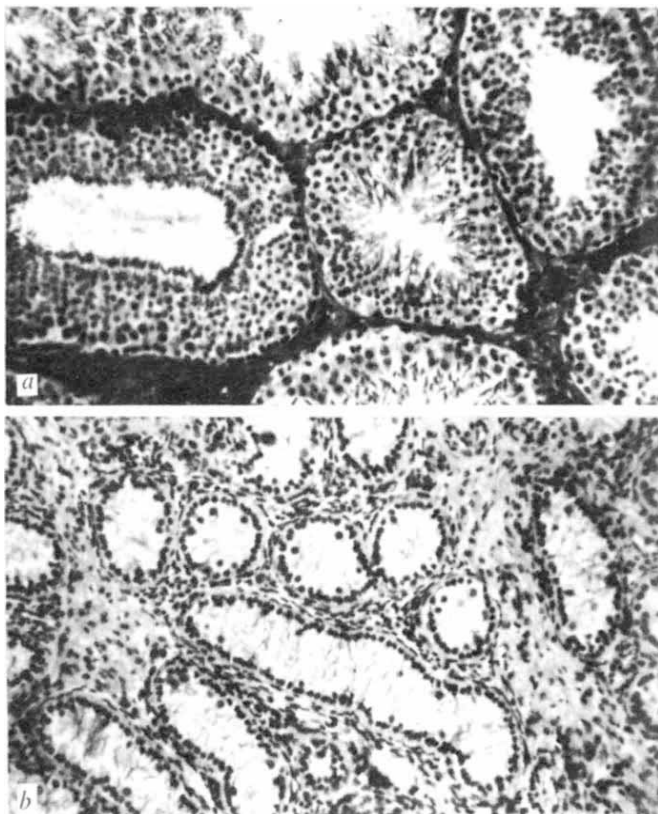


Fig. 1

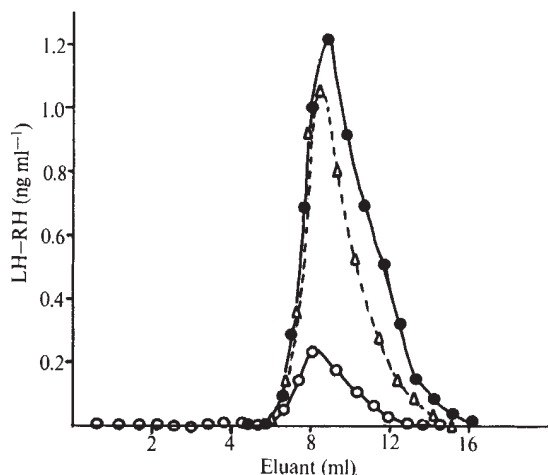


Fig. 1 Elution of immunoreactive LH-RH after gel filtration of urine extracts on 'Sephadex' G25 fine. 10×1 cm columns were eluted with 0.04 M phosphate buffer, pH 7.4, containing albumin 0.5%. (○, Extract of normal male urine; ●, same plus 5 ng standard LH-RH; △, standard LH-RH.)

this hormone capable of detecting as little as 20 pg LH-RH (ref. 2) and have attempted to apply it to the measurement of LH-RH in biological fluids.

The only situation in which we can reliably detect LH-RH in peripheral blood in man is after an intravenous test injection of LH-RH. In normal subjects there is less than 20 pg LR-RH ml^{-1} serum but, after an intravenous dose of 100 μg , concentrations can be measured for up to 2 h after injection (unpublished results of S. L. J., R. H. Greenwood and D. T. H.). There is a two-exponential decline with half-times of 5 and 45 min. As the concentration of serum LH-RH falls, LH-RH appears in the urine, about 1% of the total dose being excreted within 4 h (unpublished results of S. L. J., R. H. Greenwood, and D. T. H.).

We have attempted to assay urine from normal subjects and have detected immunoreactive LH-RH in both unextracted urine and after methanol extraction. Three approaches were used to authenticate the presence of readily detectable amounts of LH-RH in human urine: first, by dilution and recovery experiments; second, by administering appropriate physiological stimuli and observing the effect on LH-RH excretion; third, by chromatography of urine extracts in two different physical separation systems with comparison of the mobility of urine LH-RH with that of standard synthetic peptide (Hoechst).

The radioimmunoassay was essentially as described elsewhere² except that a coated-tube method was not used, the antibody-bound radioactivity being precipitated with ethanol (1.5 ml). Dilution curves of urine LH-RH were parallel to those of standard for both extracted and unextracted urine and recoveries of added LH-RH were quantitative (Table 1).

The effect of stimulating LH-RH concentrations in the urine of normal adult males and females with amenorrhoea is shown in Table 2. Clomiphene, which acts on the hypothalamus to stimulate release of LH-RH, caused an increase in LH-RH excretion in urine.

Confirmation of the identity of LH-RH in urine was

Table 2 Urine LH-RH Excretion during Clomiphene Administration (100 mg every 12 h for 5 d)

	Subjects				
	1	2	3	4	5
	LH-RH excretion ($\mu\text{g d}^{-1}$)				
Before	0.57	1.7	2.0	0.39	0.47
During clomiphene	1.52	2.2	2.6	0.80	1.4
Two days after clomiphene	1.1	1.3	1.8	0.38	0.66

Subjects 1, 2 and 3 were normal men; subjects 4 and 5 were women with amenorrhoea.

given by chromatography of methanol extracts of normal male urine. The equivalent of 1.5 ml of urine was used in each case. Silica gel thin-layer chromatography was performed on Merck precoated plates (solvent system: chloroform, methanol, water, acetic acid: 60, 45, 10, 5, by volume). After development, 0.5 cm fractions of the plates were eluted with ethanol and assayed for LH-RH content. The urine extract contained a single spot of immunoreactive LH-RH, R_F 0.43; there was also a single spot after chromatography of an equivalent extract with 5 ng LH-RH added, the R_F was 0.45 and that of standard LH-RH itself, 0.435.

Similar extracts and standards were purified by gel filtration on 'Sephadex' G25 fine in 10×1 columns eluted with the assay buffer (0.04 M phosphate, pH 7.4 with albumin 0.5%). Fractions were assayed for LH-RH. The elution patterns are shown in Fig. 1 and indicate identical mobility of urine LH-RH and standard LH-RH although there is a tendency for tailing with the larger amounts. LH-RH has been found to chromatograph atypically on 'Sephadex' and to be prone to absorption².

These results constitute the first authenticated report of the presence of hypothalamic releasing hormones in the urine of human subjects. We have also recently measured thyrotropin-releasing hormone (TRH) in human urine (unpublished results of S. L. J., H. M. F. and A. G.). Radioimmunoassay of urine samples should thus be of importance in the study of hypothalamic function and the control of the pituitary gland in both normal and pathological states.

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S. L. JEFFCOATE
D. T. HOLLAND

Department of Chemical Pathology,
St Thomas's Hospital,
London SE1

H. M. FRASER
A. GUNN

Department of Surgery,
University of Dundee,
Dundee DD1 4HN

Received March 7, 1973.

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Table 1 Recovery of Standard LH-RH added to Urine before Assay

LH-RH added (ng ml^{-1} urine)	No. of samples	Recovered LH-RH (ng) (mean)	% recovery ($\pm$ s.d.)
0.2	8	0.19	95 $\pm$ 9
1	8	1.03	106 $\pm$ 10
5	8	5.2	104 $\pm$ 8

Haemoglobin Synthesis during Human Foetal Development

IN man foetal haemoglobin (Hb F, $\alpha_2\gamma_2$), which is the main respiratory protein throughout intrauterine life, is almost completely replaced by adult haemoglobin (Hb A, $\alpha_2\beta_2$) during the first 6 months after birth. The mechanism of the switch from γ to β -chain production is unknown. In intra-

uterine life erythropoiesis occurs first in the yolk sac, then in the liver and spleen and finally in the bone marrow¹. Hb A production occurs at a low level from about the ninth to twelfth week of gestation²⁻⁶ and there is evidence that foetal liver can synthesize both Hb A and F^{4,7}. It is not known, however, whether the switch from Hb F to Hb A production is synchronous in different foetal organs, which might be expected if it were hormonally controlled, or whether there are local organ-specific differences in the rate of change from Hb F to A production. To examine this problem, and to obtain further information about the pattern of Hb A production in early intrauterine life, we have examined Hb synthesis in foetal organs at different stages of development.

Haemoglobin synthesis was examined in normal foetuses of 8, 13, 15 and 16 weeks' gestation, and in three anencephalic foetuses of 28, 32 and 34 weeks' gestation. Blood samples were obtained by cardiac puncture and bone marrow was extracted from the ribs and sternum by injecting heparinized phosphate-buffered saline (NaCl, 0.03 M; K₂HPO₄, 0.07 M; KH₂PO₄, 0.0025 M) into the bones, after which they were split longitudinally and the remaining marrow scraped out. Cell suspensions of liver and spleen were obtained by slicing the tissues into small pieces and homogenizing them gently with a glass rod. The resulting suspension was decanted from the larger fragments and strained through fine gauze to trap the smaller cell clumps. The morphological appearances of all the samples were examined by preparing standard Giemsa-stained smears.

After washing once in phosphate-buffered saline the samples were suspended in a mixture of 50% medium 199 (Glaxo Laboratories), 50% AB serum, containing 100 units ml⁻¹ penicillin and 0.5 mg ml⁻¹ streptomycin. Each tissue was incubated with 50 μ Ci ³H-leucine for 24 h at 37° C in an atmosphere of 95% air/5% CO₂. At the end of the incubation the cells were washed three times in saline (NaCl, 0.03 M; KCl, 0.005 M; MgCl₂·6H₂O, 0.0074 M), lysed by freezing and thawing and the membranes removed by centrifugation at 26,000g for 30 min. In the younger foetuses (13–16 weeks), where no peripheral blood could be obtained and the haemoglobin content of each tissue was low, 25 mg of haemoglobin from an equal mixture of adult and cord blood lysates was added to all samples. In the older foetuses, blood, liver and spleen samples provided sufficient haemoglobin and autologous blood was available as "carrier" for the marrow samples. After dialysis against 0.05 M Tris-HCl, pH 8.0, the lysates were applied to DEAE 'Sephadex' A 50 columns and Hbs A, F and F₁ separated using a 0.05 M Tris-HCl gradient, pH 7.8 to 7.0 (ref. 8). The total radioactivity incorporated into the purified haemoglobins was determined in two ways. First the Hb A and Hb F and F₁ peaks were pooled, the volumes measured and a 0.5 ml sample was counted in 10 ml Bray's solution⁹, with correction for quenching using an internal standard. The pooled fractions were concentrated *in vacuo* and converted to globin by acid acetone precipitation. The globin was dissolved in 0.5% HCOOH and a small sample counted in Bray's solution. Suitable corrections were made for the number of leucine residues in the β and γ chains. To check the purity of these haemoglobins the remainder of the globin was separated into its constituent chains¹⁰. The Hb F and F₁ fraction contained only radioactive α and γ chains while the Hb A samples showed incorporation into the α and β chains (Fig. 1).

The relative amounts of Hbs F and A synthesized in foetal haemopoietic tissues at different stages of development are given in Table 1, which indicates that there is no gross difference in the amount of each haemoglobin synthesized by the different tissues. The data obtained from the marrow samples in the 13–16 week foetuses must be interpreted with caution, however, as it is believed that haemopoiesis in the marrow does not begin until the fourth or fifth month of gestation¹. Indeed, haemoglobin synthesis in the 13 week marrow sample may have been attributable to peripheral blood contamination as

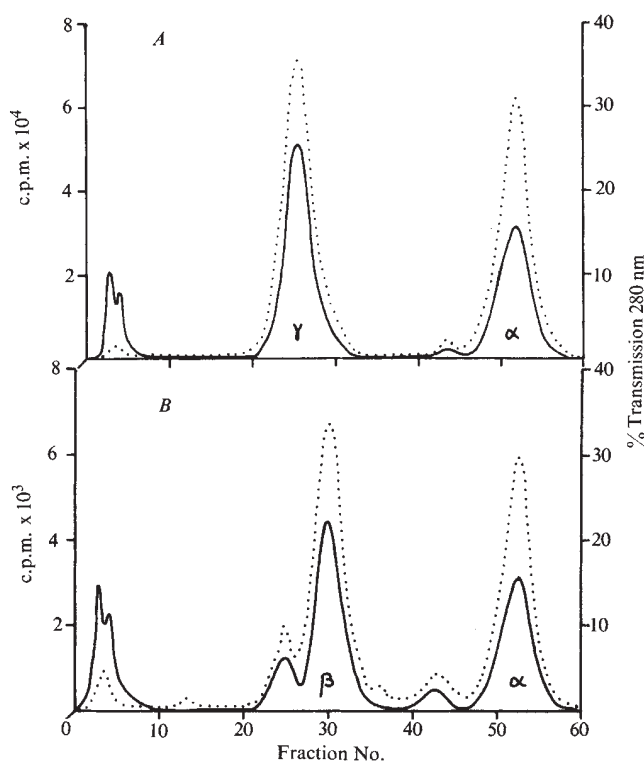


Fig. 1 Haemoglobin synthesis in the liver of a 16 week foetus. After incubation Hbs F₁, F and A were separated by DEAE 'Sephadex' chromatography. The fractions contained Hb A and Hb F and F₁ were separately pooled, concentrated and converted to globin. The chains were separated by CM chromatography in 8 M urea. A, Chain separation of the isolated Hb F and F₁ fractions showing the distribution of radioactivity in α and γ chains. B, Isolated Hb A fraction showing distribution of radioactivity in α and β chains.

no young erythroid precursors were seen on stained smears. In the marrows from the 14 and 16 week foetuses, however, erythroid cells, though few in number, were seen at all stages of maturation, unlike the peripheral blood which contained only late normoblasts. It is possible that the presence of erythroid cells in the marrow at this early stage of development results from "seeding" by erythroid precursors of liver origin. It is impossible to determine how much of the total haemoglobin synthesized by the spleen and liver samples is attributable to the peripheral blood which they contain. In the 13–28 week foetuses this is unlikely to affect the results as these organs were highly erythroid, but at 32 and 34 weeks the erythroid content of the spleen and liver was much reduced. Haemoglobin synthesis in the late normoblasts of the peripheral blood presumably reflects the situation in their tissue of origin and hence depends on the relative contribution of the marrow, liver, and spleen to the circulating normoblast population. Disparities in the amount of haemoglobin A synthesized by each tissue would thus be reduced by peripheral blood contamination. With these provisos, however, there

Table 1 Percentage Haemoglobin A Synthesized in the Haemopoietic Tissues of 13–34 Week-Foetuses, as Measured by the Total Incorporation of ³H-Leucine into each Haemoglobin Fraction

Tissue	Gestational age and crown-rump length					
	13 weeks 125 mm	14 weeks 120 mm	16 weeks 130 mm	28 weeks —	32 weeks —	34 weeks —
Blood	5.2	—	—	9.3	12.6	10.1
Marrow	7.4	6.5	15.6	9.7	11.9	9.8
Liver	8.1	6.1	9.9	9.0	12.0	10.8
Spleen	7.6	6.1	9.7	9.7	13.0	11.7

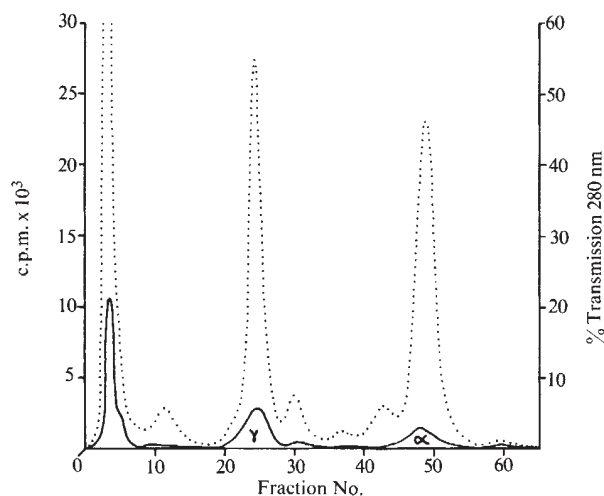


Fig. 2 Haemoglobin synthesis in the liver of an 8 week foetus. The details of this experiment are given in the text. After incubation the cells were washed and lysed and globin prepared from the small amount of haemoglobin present. Four radioactive peaks were observed and the total incorporation was as follows: (c.p.m.) γ , 65,725; post γ (shown to be β), 8,100; pre α , 10,475; α , 80,825. The identity of the chains was confirmed by methods outlined in the text.

appeared to be no gross difference between the rates of Hb A and Hb F production in different foetal organs.

Confirmation of these results was obtained in the three older foetuses where either no carrier haemoglobin was required or autologous carrier was available, making it possible to measure the specific activity (SA) of haemoglobin fractions, as well as the total radioactivity incorporated. The SAs of the Hb A and Hb F and their constituent globin chains obtained from the 28 week foetus are shown in Table 2 and the results from the three foetuses are summarized in Table 3. The closeness of the ratios obtained from the four tissues is again evident. In the 28 and 34 week foetuses the ratios are almost

Table 2 Relative Specific Activities of ^3H -Leucine of Hbs A and F and their Constituent Globin Chains in a 28 Week Anencephalic Foetus

Tissue	Haemoglobin (c.p.m. mg ⁻¹)	Hb A/Hb F	Globin (c.p.m. mg ⁻¹)	γ/β
Blood	A 20,600	1.07	α ^A 20,040	0.92
			β 19,054	
	F 19,275		α ^F 20,099	
			γ 20,730	
Marrow	A 6,171	1.07	α ^A 5,845	1.17
			β 6,564	
	F 5,816		α ^F 5,453	
			γ 5,626	
Liver	A 4,944	1.01	α ^A 4,817	0.97
			β 5,032	
	F 4,886		α ^A 4,817	
			γ 5,167	
Spleen	A 3,644	1.08	α ^A 3,345	0.96
			β 3,289	
	F 3,389		α ^F 3,312	
			γ 3,424	

Table 3 Ratios of the Specific Activities of Haemoglobins A and F and their Constituent β and γ Chains in Three Anencephalic Foetuses

Tissue	Gestational age (weeks)					
	28	32	34			
	A/F	β/γ	A/F	β/γ	A/F	β/γ
Blood	1.07	0.92	1.42	1.50	1.01	0.94
Marrow	1.07	1.17	1.35	1.48	1.04	1.11
Liver	1.01	0.97	1.29	1.42	1.01	1.06
Spleen	1.08	0.96	1.41	1.61	1.50*	1.05

* Hb A fraction was contaminated.

Table 4 ^{14}C and ^3H Incorporation into β Chain Peptides after Tryptic Digestion of Uniformly Labelled ^{14}C β Chains mixed with ^3H -Labelled Post γ Chains Peak*

β Chain peptide number	No. of leucine residues	^{14}C (c.p.m.)	^3H (c.p.m.)	$^{14}\text{C}/^3\text{H}$
1	1	33	57	0.57
2	1	135	294	0.46
3	1	121	224	0.54
4	2	171	439	0.39
5 $_{ox}$	1	76	139	0.55
6	0	0	0	—
7	0	0	0	—
8	0	0	0	—
8-9	4	159	340	0.47
9		302	679	0.45
13	0	0	0	—
14	1	75	139	0.54
15	0	0	0	—

*The latter was obtained by incubating the liver of an 8 week foetus with ^3H -leucine and separating the globin chains as indicated in the text.

exactly one suggesting that the amount of haemoglobin A synthesized is the same as that present in the peripheral blood and that it is not increasing. In the 32 week foetus the SA of the Hb A was slightly greater than that of the Hb F, suggesting that the main switchover had started. Thus it appears that from the twelfth to thirty-fourth week Hb A synthesis is active and comprises about 5–10% of the total haemoglobin produced during this period.

To study haemoglobin synthesis in early foetal life liver cells were obtained from an 8 week foetus measuring 50 mm from crown to rump. The liver was incubated with ^3H -leucine as before and the small amount (about 5 mg) of haemoglobin obtained after lysis converted to globin. The chains were separated on CM-cellulose and the radioactive incorporation measured. Figure 2 shows that although most of the ^3H incorporation was into γ and α chains a small peak corresponding to the position of the β chain was also observed. To determine whether this peak was β chain it was mixed with uniformly labelled ^{14}C - β chains, prepared by incubating reticulocyte-rich adult blood with ^{14}C -leucine, in a ^{14}C to ^3H ratio of 0.45. The chains were then digested with trypsin and fingerprinted¹⁰ and the ^{14}C to ^3H ratio for each peptide was calculated. The ratios ranged from 0.39 to 0.57 (mean 0.49) (Table 4) and the labelling of the peptides was consistent with the post γ peak being β chain. A similar method was used to examine the small radioactive peak which chromatographed immediately before the α chain (Fig. 2); like the similar fraction in adult lysates this behaved in an identical manner to normal α chains. No components with the properties of ϵ chains were observed; presumably ϵ chain synthesis has already stopped by the eighth week. The ζ chains of Hb Portland, another minor haemoglobin of intrauterine life¹¹, would not have been isolated as they cochromatograph with the γ chain in these conditions¹².

These results indicate that Hb A is present as early as the eighth week of gestation and that its relative rate of production

remains relatively constant until at least 32–34 weeks; this finding is in agreement with a model proposed by Kleihauer¹³. The relative amounts of Hb A and F produced appear to be equal throughout all the sites of foetal erythropoiesis during this period of development; that is, the switch appears to be quite synchronized. These findings are compatible with a model in which the relative rates of Hb F and A production are under general control rather than the influence of local tissue control mechanisms. This observation is of particular interest in view of recent evidence regarding the reactivation of Hb F production in some women during early pregnancy and the suggestion that this could result from the action of an agent produced either by the foetus or placenta¹⁴.

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W. G. WOOD
D. J. WEATHERALL

Department of Haematology,
University of Liverpool,
Liverpool L69 3BX

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Significance of Lead Isotope Composition in Blood

THERE have been several attempts^{1–6} to identify the sources of lead in the air and vegetable or animal tissue by analysis of stable isotopes. Blood sampling is the easiest means of conducting a large scale investigation of lead in the human body. Here I report some measurements as part of an exploration of the feasibility of such a programme.

In collaboration with the Health Department of Dallas, Texas, we measured the ratios of lead isotopes in the blood of residents, in particulate airborne lead and in emissions from two smelters in residential districts in southern Dallas which reprocess discarded batteries. Particulate material was collected on fibreglass filters from which lead was leached with hot 70% nitric acid. About 60 µg of lead was processed. A blank filter contained 0.4 p.p.m. of leachable lead. About 30 ml of blood was drawn and decomposed by boiling with 70% nitric acid. Lead was separated by the method of Tatsumoto⁷ and concentrations were determined by stable isotope dilution using a pure ²⁰⁶Pb spike. Procedural blanks were consistently less than 0.005 µg Pb. Isotope ratios were

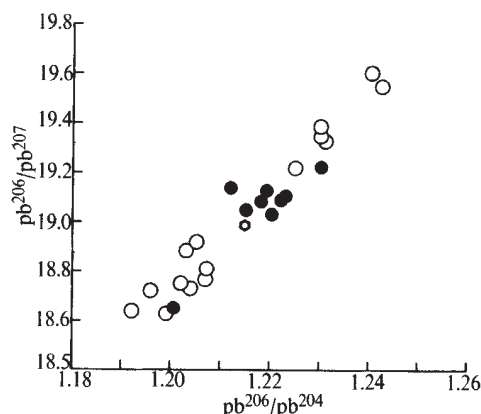


Fig. 1 Isotope ratios of lead in petrol collected in Dallas on July 14, 1972 (○), and of airborne particulate lead collected at various stations on July 18, 1972 (●). ○, Mean of the gasoline.

measured on a 12-inch Nier type mass spectrometer, an emitter of silica gel and phosphoric acid being used to produce ions⁸. Standard deviations were about 0.2% of the ratios measured.

The isotope ratios of lead in samples of petrol purchased in Richardson, northern Dallas, on July 14, 1972, were compared with those of airborne particulate samples collected during the 24 h period July 17–18 at nine stations in Dallas city using a 'Hi-Vol' sampling apparatus (General Metal Works, Cleves, Ohio). The isotope ratios measured in the particulate material were, with one exception, closely grouped but the petrol ratios fell into two groups (Fig. 1). The average for the petrol samples was similar, but did not exactly correspond to that of the particulate material, probably because of insufficient sampling of the petrol, the uncertain weighting of the mean to account for the amount of lead in each brand and the volumes, of each brand sold, both premium and regular.

One site was selected as typical and samples collected at monthly intervals from July 1971 to November 1972 were analysed. The ²⁰⁶Pb/²⁰⁴Pb ratio is plotted against time in Fig. 2. Since November 1971 the ratio has been consistently greater than 19. Samples collected at the property line of the smelters have been analysed and, from the few analyses available (Fig. 5), it seems that the ²⁰⁶Pb/²⁰⁴Pb ratio in smelter emissions (usually a run of 4 h) is remarkably constant.

Samples of blood from a number of male employees and students at the University of Texas at Dallas were taken during August 1972 and were analysed for lead concentration and isotope ratios (Table 1). None of the subjects claimed any abnormal exposure to lead during their lives and all lived in the northern part of the city, at least 10 miles from the smelters. The isotope ratios in the blood of seven of the subjects formed a broad group distinct from those of the airborne

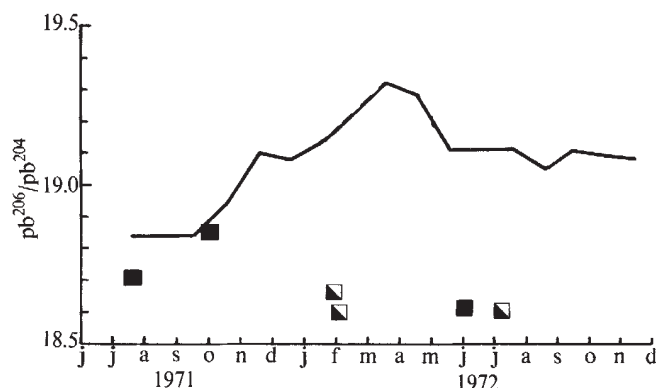


Fig. 2 ²⁰⁶Pb/²⁰⁴Pb ratio of airborne particulate lead over Dallas as measured from one station at monthly intervals (—). Also shown are ²⁰⁶Pb/²⁰⁴Pb ratios from two smelters in the area (■, ■).

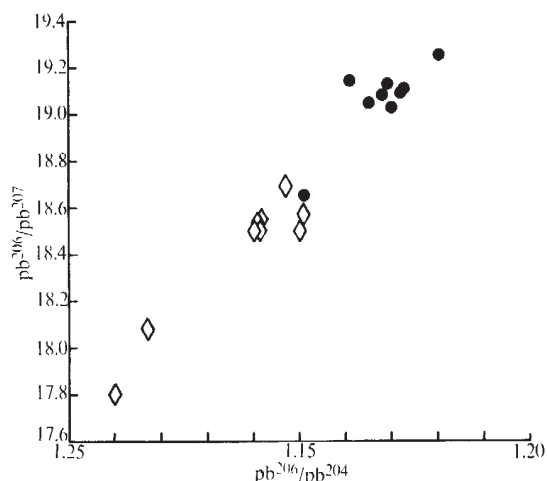


Fig. 3 Isotope ratios of airborne particulate lead over Dallas on July 18, 1972 (●), and blood of Dallas residents (◇) drawn in August 1972.

particulate material (Fig. 3). Two other subjects, one (R. A.) Australian, the other (W. M.) South African, had different ratios. Both have lived in Texas continuously for more than 8 yr. Of the other seven, one (E. F.) is Hungarian.

The different ratios encountered in two of the foreign born subjects suggest that the isotope ratios of lead in blood reflect past, and not present, exposure and that they respond slowly to changes in the isotope ratios of ingested lead. The blood of W. M. was drawn again on December 21, 1972, and that of his American wife (of four years), J. M., on December 27, 1972. The isotope ratios of lead in his blood did not change significantly in 4 months (Table 1) but the two sets of isotope ratios differed widely (Fig. 4). The isotope ratios of lead in the blood of another South African (B. C.) who has lived in North America for 5.5 yr are also distinct from those in the blood of his American wife, in spite of 3 yr of marriage. As each husband and wife have occupations and eating habits which ensure that each has been exposed to essentially the same sources of lead during their marriage, the difference in isotope ratios in their blood can be attributed to different exposures to lead before marriage. It would seem that lead in the blood continuously mixes with a large reservoir of lead elsewhere in the body, presumably in the skeleton.

It can be demonstrated that long times of response are consistent with available data regarding the daily uptake and body burden of lead. I shall suppose that a certain number of

atoms of lead enters the blood each day, mixes with the lead already present in the body and then the same number as entered the blood is removed in the urine, so as to maintain the total number of atoms of lead in the body constant. If i_0 is the fractional abundance of an isotope in the lead initially contained in the body, j is the fractional abundance of the same isotope in the lead absorbed into the blood each day, and k is the ratio of the number of mol of lead absorbed into the blood each day to the number of mol of lead in the body. It can be shown that, after mixing on the n th day, the fractional abundance of the isotope in the lead contained in the body will be

$$i_n = i_0 + jk \sum_{m=0}^{n-1} (1+k)^m / (1+k)^n$$

Blokker⁹ states that about 40 μ g of lead is absorbed into the blood each day and that the average body burden is 112 mg. These data suggest a value of k of about 3.6×10^{-4} . The change in the $^{206}\text{Pb}/^{204}\text{Pb}$ ratio in blood initially with ratios, $^{206}\text{Pb}/^{204}\text{Pb} = 17$, $^{207}\text{Pb}/^{204}\text{Pb} = 15.5$ and $^{208}\text{Pb}/^{204}\text{Pb} = 38$ as a result of the daily absorption of lead with ratios, $^{206}\text{Pb}/^{204}\text{Pb} = 19$, $^{207}\text{Pb}/^{204}\text{Pb} = 15.6$ and $^{208}\text{Pb}/^{204}\text{Pb} = 40$, was calculated for values of k equal to 8×10^{-4} , 4×10^{-4} , 2.67×10^{-4} and 2×10^{-4} . For a daily uptake of 40 μ g Pb these values of k correspond to body burdens of 50, 100, 150 and 200 mg Pb, which cover the range reported by Blokker. Figure 5 shows that response times are of the order of tens of years.

The isotope ratios of lead in the blood of adults respond

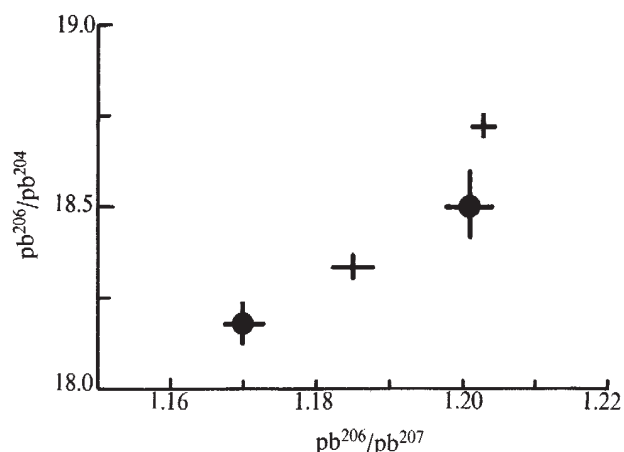


Fig. 4 Isotope ratios of blood of spouses W. M. and J. M. (+) and B. C. and T. C. (●). Bars represent 95% confidence limits.

Table 1 Isotope Ratios and Concentrations of Lead in Blood (μ g per 100 g)

	Pb	$^{206}\text{Pb}/^{204}\text{Pb}$	$^{207}\text{Pb}/^{204}\text{Pb}$	$^{208}\text{Pb}/^{206}\text{Pb}$	Date (1972)
R. A.	*	17.8	1.16	2.09	August 3
E. F.	*	18.5	1.19	2.05	August 3
W. M.	*	18.11	1.167	2.085	August 3
T. B.	12.5	18.5	1.20	2.06	August 18
J. C.	17.5	18.54	1.191	2.051	August 18
M. K.	13.5	18.57	1.201	2.036	August 18
W. M.	21.7	18.05	1.164	2.079	August 18
J. N.	16.4	18.69	1.197	2.043	August 18
S. R.	19.6	18.50	1.193	2.049	August 18
D. Y.	21.8	18.54	1.191	2.048	August 18
Husband-wife comparisons					
W. M.	21.3	18.18	1.170	2.079	December 21
J. M.†	11.3	18.5	1.201	2.027	December 27
B. C.	12.4	18.33	1.185	2.058	December 28
T. C.†	9.5	18.72	1.203	2.041	December 28

* Concentration data considered unreliable.

† Wife.

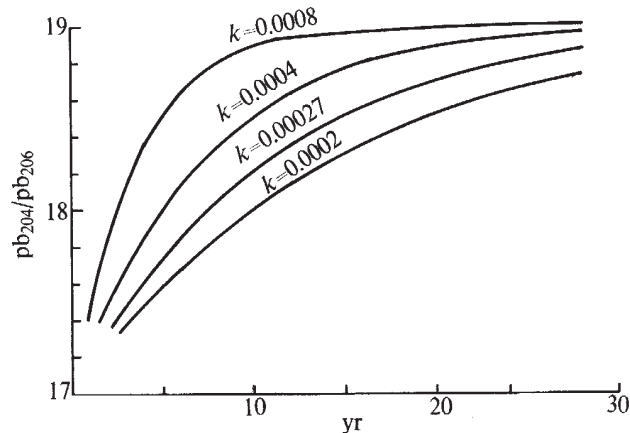


Fig. 5 Change in the $^{206}\text{Pb}/^{204}\text{Pb}$ ratio of lead in blood from an initial value of 17 because of the absorption of lead with a $^{206}\text{Pb}/^{204}\text{Pb}$ ratio of 19. Curves are shown for various values of k .

slowly to changes in the ratios of the lead that is ingested. Isotope tracer studies to measure the uptake of lead from pollutants are therefore best attempted on children, because, as a child grows and his bones calcify, lead moves from his blood into his skeleton. The isotope ratios of lead in his blood will therefore be fairly representative of the lead to which he has been exposed, irrespective of any exchange of isotopes with the skeleton.

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W. I. MANTON

*Institute for Geological Sciences,
University of Texas at Dallas,
PO Box 30365,
Dallas,
Texas 75230*

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Aggregation of Human Platelets by Bovine or Human Factor VIII: Role of Carbohydrate Side Chains

RECENT work^{1,2} has demonstrated that bovine factor VIII, not bovine fibrinogen, aggregates human platelets. This aggregation can occur in two waves, the first being independent of

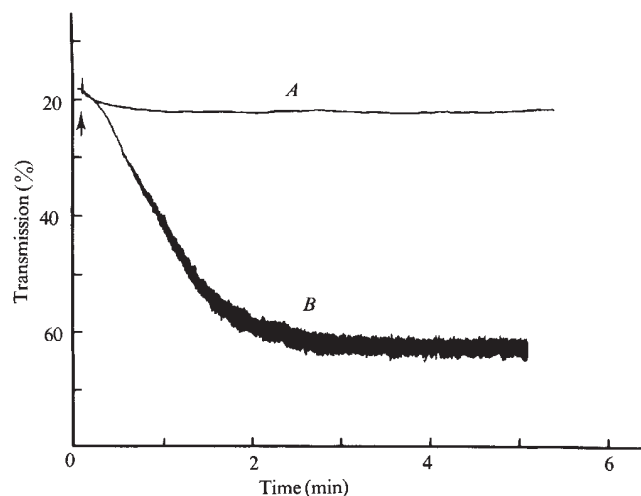


Fig. 1 One millilitre of bovine factor VIII ($0.4 \text{ units ml}^{-1}$ 0.025 M Tris- 0.025 M trisodium citrate- 0.2 M ϵ -aminocaproic acid buffer, $\text{pH } 7.4$) was incubated for 3 h at 37°C with either 0.16 ml 0.03 M Tris buffer, $\text{pH } 7.0$, or the same buffer containing fifteen units of galactose oxidase. Factor VIII was measured as previously described¹⁰. The arrow indicates the moment of the addition of 0.2 ml of the mixture to 0.8 ml citrated human platelet-rich plasma ($300,000 \text{ platelets } \mu\text{l}^{-1}$) in a Born aggregometer. *A*, Mixture containing galactose oxidase; *B*, mixture containing buffer. A curve identical to *B* was obtained when the bovine factor VIII-galactose oxidase mixture was tested without preincubation.

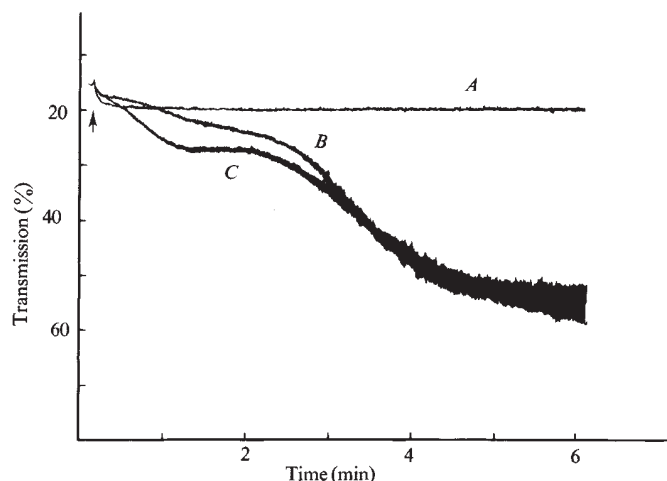


Fig. 2 To 0.75 ml human factor VIII solution ($1.5 \text{ units ml}^{-1}$), 0.25 ml neuraminidase (4 units ml^{-1} isotonic saline) was added. Neuraminidase was type VI from *Clostridium perfringens*, Sigma Chemical Company, St Louis, Missouri; two batches have been used. The human factor VIII-neuraminidase mixture was preincubated at 37°C . At different moments, 0.2 ml was added to 0.8 ml citrated human platelet-rich-plasma ($300,000 \text{ platelets } \mu\text{l}^{-1}$) in a Born aggregometer. *A*, Preincubation for 1 min; *B*, preincubation for 60 min; *C*, preincubation for 90 min.

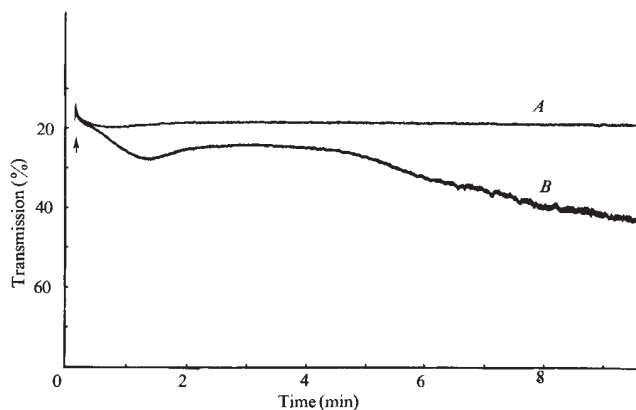


Fig. 3 0.75 ml human factor VIII solution ($2.15 \text{ units ml}^{-1}$) was mixed with 0.16 ml of galactose oxidase solution ($125 \text{ units ml}^{-1}$ 0.03 M Tris buffer, $\text{pH } 7.0$) or of buffer; to both systems 0.25 ml neuraminidase (four units ml^{-1} isotonic saline) was added. Both mixtures were incubated at 37°C for 15 min. 0.2 ml samples were then blown into 0.8 ml citrated human platelet-rich-plasma ($300,000 \text{ platelets } \mu\text{l}^{-1}$) in a Born aggregometer. *A*, Human factor VIII+galactose oxidase+neuraminidase; *B*, human factor VIII+buffer+neuraminidase.

release of platelet adenosine-5'-diphosphate. Bovine factor VIII is rich in carbohydrate: it contains 11% hexoses (mannose and galactose, in a ratio of 1 to 3), 2% sialic acid and 7% hexosamine³. Carbohydrate side chains would play a critical role in collagen-platelet adhesion and subsequent aggregation; a substrate-enzyme complex⁴ would be formed between side chains of collagen containing galactose⁵ but not terminated by sialic acid and sialyl transferase located on the platelet membrane⁶. Oxidation of the galactosyl residues in collagen abolishes platelet aggregation⁵. We wondered whether a similar mechanism would initiate platelet aggregation by bovine factor VIII.

Bovine factor VIII devoid of fibrinogen was prepared by gel filtration of a commercial factor VIII preparation (S. Maw and Sons, New Barnet) through 6% agarose ('Biogel' A-5m, Biorad Laboratories, Richmond, California) as described previously². Galactose oxidase Type 1 (*Dactylum dendroites*, 30 units mg^{-1} solid) was obtained from Sigma Chemical

Company, St Louis, Missouri. Figure 1 shows that exposure of bovine factor VIII to galactose oxidase completely abolished its aggregating property. This suggests that interaction of galactose-containing side chains in bovine factor VIII with the platelet membrane is the trigger for the platelet aggregation brought about by this protein.

Human factor VIII devoid of fibrinogen was prepared by gel filtration of chylomicron-poor cryoprecipitate through a 0.9×30 cm column containing 6% agarose; elution was performed with 0.03 M Tris buffer, pH 7.0. Factor VIII, eluted at the void volume, has no platelet aggregating activity. Figure 2, however, shows that human factor VIII, preincubated with neuraminidase, produces strong platelet aggregation, occurring in two waves. When human factor VIII is incubated simultaneously with galactose oxidase and neuraminidase (Fig. 3), no platelet aggregation is observed. It thus appears that human factor VIII interacts with platelets when galactose-containing side chains not terminated by sialic acid are exposed.

Angiohaemophilia (von Willebrand's disease) is characterized by lack of immunological and biological factor VIII activity⁷ and by defective platelet adhesion *in vivo*⁸ and *in vitro*⁹. This study may provide a clue as to the reason for the abnormal platelet adhesion-aggregation reaction in this disease.

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J. VERMYLEN
M. B. DONATI
G. DE GAETANO
M. VERSTRAETE

Laboratory of Blood Coagulation,
Medical Research Department,
University of Leuven,
Kapucijnenvoer 35, B-3000 Leuven,
Belgium

Received March 12, 1973.

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Morphine Tolerance and Supersensitivity to 5-Hydroxytryptamine in the Myenteric Plexus of the Guinea-pig

ELECTRICAL stimulation of the isolated guinea-pig ileum or its longitudinal muscle with attached myenteric plexus releases acetylcholine (ACh) and causes a muscle twitch. The twitch tension is decreased by morphine, as is the output of ACh¹⁻⁵. This effect of morphine is caused by an action of the drug upon the myenteric plexus. Investigations in several laboratories^{3,6-8} have shown that the morphine receptors in this neural network are like those in the central nervous system in all the following essentials: (1) The effective concentrations of morphine are very low, of the order of 20–100 nM. (2) The rank order of potencies of various narcotics is the same as for analgesia and other typical central actions over a very wide range of concentrations. (3) The response to narcotics is stereospecific for the D(–) isomers.

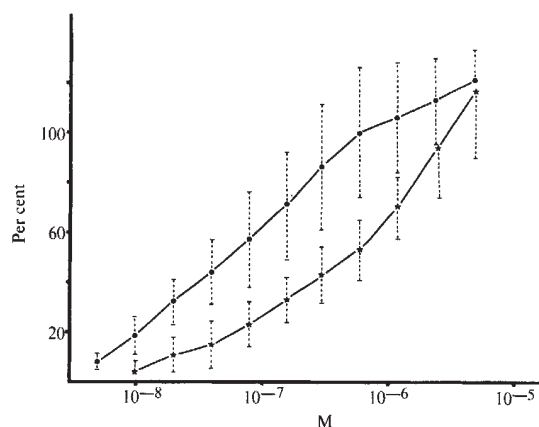


Fig. 1 Dose-response curves for 5-HT. Data are for control strips (★) and morphine-tolerant preparations the third day after pellet implantation (●). 5-HT was added to the bath 10 s after turning off the electrical stimulation. The ordinates represent tension in % of the preceding electrically induced twitches (maximal stimulation). Each point is the mean of six to eight tests, on tissues from different animals. Vertical bars indicate standard errors.

(4) Narcotic antagonists, especially the pure antagonists like naloxone, block or reverse the agonist effects. (5) Tolerance to morphine develops in this tissue *in vivo*, as we have shown^{9,10}.

Theories have been advanced which account for drug tolerance and dependence by a change in the number or properties of the drug receptors¹¹⁻¹⁴ or of receptors for an endogenous neurotransmitter^{15,16}. Our recent demonstration of morphine tolerance in the ileum of the guinea-pig made tolerant to this drug provided a way of testing directly whether or not tolerance is associated with a change in sensitivity to any neurotransmitter.

Guinea-pigs were made tolerant and dependent by subcutaneous implantation of four morphine pellets (75 mg each). After 3 d, a high degree of tolerance and dependence had developed, as measured by the lack of hypothermic effect of a morphine injection and the abstinence syndrome precipitated by naloxone¹⁰. The longitudinal muscle-myenteric plexus preparation from control and tolerant animals was prepared as described by Kosterlitz *et al.*¹⁷. We shall call this preparation "muscle strip", or simply "strip". The strip was suspended in Krebs bicarbonate Ringer solution in a 5 ml bath, and washed repeatedly at intervals of 5–10 min for at least 1 h before adding any test substance. Field stimulation (0.1 Hz, 0.5 ms) was applied by means of a platinum ring, at a voltage sufficient to produce a maximum isometric twitch (about 80 V d.c.). The twitch tension was measured with a Grass FT.03C transducer and a Grass polygraph. The resting tension was adjusted (usually 0.4–0.6 g) to yield a maximum twitch tension (range 1.5–2.5 g). In control experiments, this washing procedure was sufficient to remove all trace of a morphine effect after morphine had been added to the bath at the outset. 5-Hydroxytryptamine (5-HT) was tested by adding it to the bath 10 s after turning off the electrical stimulator.

As we reported elsewhere¹⁰, electrically stimulated muscle strips from tolerant-dependent guinea-pigs were tolerant to the inhibitory action of morphine, and also had decreased sensitivity to the inhibitory actions of adrenaline, isoproterenol, and dopamine; their sensitivity to the spasmogenic action of ACh was, however, unchanged. We now report a large increase in sensitivity to 5-HT associated with morphine tolerance. 5-HT has a spasmogenic effect in the normal strip. At 3×10^{-6} M, the twitch tension was about the same as obtained by electrical stimulation, as shown in the control log dose-response curve at the right of Fig. 1. Strips from morphine-tolerant animals were about ten times more sensitive to

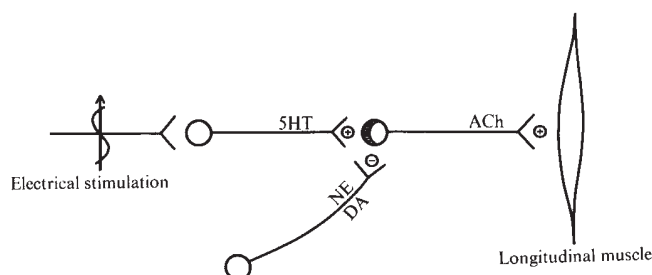


Fig. 2 Possible neuronal interactions in the longitudinal muscle strip-myenteric plexus preparation. Excitatory $\oplus$ actions represented by 5HT-containing (5HT) and cholinergic (ACh) neurones. Inhibitory $\ominus$ actions represented by dopaminergic (DA) or noradrenergic (NE) neurones. The hatched field at the post-ganglionic site indicates receptors sensitized to 5-HT in tolerant preparations.

5-HT, as shown by the shift of the curve to the left. This degree of supersensitivity was very nearly the same as the degree of tolerance to morphine¹⁰. Naloxone, added to the bath at 225 nM before 5-HT challenge, was without effect in control or tolerant strips.

The findings presented here, together with those published earlier¹⁰, while by no means decisive, do suggest a coherent and parsimonious explanation of the acute effect of morphine and of tolerance to morphine in this tissue. Exogenous 5-HT, like electrical stimulation, causes contraction of the longitudinal muscle, which is blocked by atropine¹⁸. It seems possible that 5-HT could play a physiological role as an excitatory transmitter in the myenteric plexus, leading to cholinergic stimulation of the muscle. Indirect evidence supports the suggestion. First, the intact preparation is much more sensitive to 5-HT than one from which the plexus has been removed⁴. Second, recent histochemical evidence strongly indicates the presence of terminals containing 5-HT in the plexus¹⁹. Third, as shown by Gaddum and Picarelli¹⁸, the excitatory response to 5-HT is blocked by morphine (at "M receptors") at the same concentrations that block the electrically stimulated twitch, whereas 5-HT receptors in the muscle itself ("D receptors") are insensitive to morphine. We suppose, therefore (Fig. 2), that the myenteric plexus contains a type of serotonergic synapse, at which the post-synaptic element is the cholinergic neurone that innervates the longitudinal muscle. The acute effect of morphine could be to inhibit transmission at this synapse, thereby decreasing the output of acetylcholine and the twitch tension of the muscle.

We propose, along the lines of a recent suggestion by Vander Wende and Spoerlein²⁰, that an adrenergic (or dopaminergic) neurone could modulate transmission in an inhibitory manner at a synapse in the excitatory pathway, perhaps at the same serotonergic synapse where we think morphine manifests its action. The usual arrangement, whereby postganglionic sympathetic neurones innervate smooth muscle directly, could, of course, play a role. The finding that exogenous catecholamines decrease the output of ACh in this preparation²¹, however, strongly suggests a catecholamine action on some neural element of the plexus.

The remaining question is whether morphine acts by blocking postsynaptic 5-HT receptors, or whether it blocks transmission at the serotonergic synapse by mimicking the effect of a catecholamine or causing the release of a catecholamine. As Gyang and Kosterlitz⁵ showed that α - and β -adrenergic blockers do not interfere with the morphine effect in this tissue, it seems unlikely that morphine could act by releasing noradrenaline or by combining with noradrenaline receptors. The possibility has not yet been ruled out, however, that morphine could release dopamine, as suggested by the data of Sasame *et al.* with methadone²². Such release could involve a dopaminergic interneurone²³. Alternatively, morphine could stimulate dopamine receptors.

We propose that tolerance to morphine is produced by an increase in the number or intrinsic sensitivity of 5-HT receptors, as first suggested by Collier²⁴. Thus, the normal function of the excitatory pathway would be restored, in spite of the continued presence of morphine, and a greater concentration of morphine (or catecholamines) would be required for inhibition. Sensitization of the synapse under discussion here would accomplish this, regardless of whether morphine acted directly upon the 5-HT receptors, or indirectly through release of an inhibitory transmitter. It remains to be determined if the supersensitivity to 5-HT is brought about by an increase in the number of receptors or a change in their properties. Inhibition of tryptophan hydroxylase by morphine, followed by expansion of this enzyme²⁵, could also possibly contribute to the tolerant-dependent state.

Dependence, we believe, would result from the same change in the 5-HT receptors, as predicted on theoretical grounds^{11-13,16,24}. *In vivo*, in the tolerant-dependent state, removal of the morphine effect (as by abrupt withdrawal or naloxone), in the presence of normal vagal stimuli, would make the 5-HT supersensitivity manifest, causing hyperexcitability of the gut, as observed in the intact animal. Moreover, as shown by Wei *et al.*²⁶, a central action of naloxone apparently provokes increased vagal outflow to the gut. On the other hand, in the isolated denervated strip from the tolerant-dependent animal, morphine is removed by the extensive washing procedure. In this preparation the 5-HT supersensitivity would be revealed, but naloxone could have no further effect, in accord with our findings.

We believe this is the first demonstration of an altered sensitivity to a neurotransmitter, associated with morphine tolerance. Whether or not our finding is relevant to tolerance and dependence in the central nervous system remains to be seen.

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R. SCHULZ
A. GOLDSTEIN

Addiction Research Laboratory,
Department of Pharmacology,
Stanford University,
California 94305

Received March 8, 1973.

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Enzyme-containing Liposomes alleviate a Model for Storage Disease

THE treatment of inherited enzyme deficiencies in man can be approached in at least two ways: correction of the malfunctioning gene normally responsible for the transcription of the missing enzyme, or exogenous replacement of the missing enzyme¹. In both approaches enzymes, DNA or RNA fragments or drugs designed to replace or correct those that are missing or malfunctioning, should, after administration, reach and act in the cells where the enzyme function is important. In reaching the site of action, however, such substances could provoke immunological reactions, be incompatible with blood or vulnerable to blood enzymes, be taken up by the reticulo-endothelial system or non-diseased tissues, or even be unable to reach or penetrate target tissues.

These problems might be eradicated by the entrapment of therapeutic substances before their administration, in a general carrier which would not only protect its contents from the environment and *vice versa*, but also, because of its surface properties, direct its contents to a target tissue and facilitate uptake by diseased cells while the carrier itself is digested or otherwise eliminated.

Some of the requirements for such a carrier are satisfied by liposomes²⁻⁶. These consist of concentric lipid bilayers alternating with aqueous compartments within which water soluble substances can be entrapped^{7,8}. Experiments with enzyme-containing liposomes^{4,5} have shown that the activity of enzymes entrapped in liposomes is rendered latent; it remains so in blood after injection of such liposomes into rats and it is rapidly recovered in the liver lysosomes and spleen.

The carriage of enzymes by liposomes into the liver lysosomes could be applicable to the treatment of storage diseases in which deficiency of a specific enzyme activity (usually lysosomal) in one or more tissues leads to the accumulation of relevant substrates in the lysosomes of the affected tissues^{9,10}. It therefore seemed appropriate to test the therapeutic efficiency of liposomes as enzyme carriers in a model for storage disease.

Exposure to sucrose of mouse peritoneal macrophages¹¹ and Chinese hamster fibroblasts¹², both lacking invertase activity¹¹, leads to the accumulation of sucrose within their lysosomes which then appear as phase-lucent vacuoles in the perinuclear region. Subsequent incubation in the presence of invertase results in the uptake of invertase, hydrolysis of stored sucrose and elimination of phase-lucent vacuoles¹¹. We have investigated the possibility of using liposomes for the carriage of invertase into sucrose-loaded macrophages and fibroblasts. Invertase or heat-inactivated invertase (70–80° C for 20 min) was entrapped in liposomes composed of egg lecithin, cholesterol and phosphatidic acid (molar ratio 7: 2: 1)⁵. Unstimulated mouse peritoneal macrophages were collected¹³ from specific pathogen-free mice of both sexes (TO strain, 20–25 g) and cultured¹³ for 4 h at 37° C in 'Nuclon' Petri dishes (50 mm diameter) containing 5 ml medium 199 (Grand Island Biological Company), 20% foetal calf serum (Flow Laboratories), 100 IU ml⁻¹ penicillin and streptomycin respectively, and 0.11% sodium bicarbonate (complete medium), and three to four coverslips. Human embryo lung fibroblasts (MRC-5, twenty-

third passage) were grown for 4 d in similar conditions in the presence of 4 ml Eagle's basal medium (Grand Island Biological Company) and 10% calf serum (Biocult Laboratories).

Sucrose loading of macrophages ($1.2\text{--}2.5 \times 10^6$ cells per dish) and fibroblasts (5×10^5 cells per dish) and subsequent exposure to invertase-containing liposomes were carried out as follows. In a typical experiment cells in six dishes were exposed to complete medium containing 10 mg sucrose ml⁻¹ occasionally mixed with 12.5 μ Ci U-¹⁴C-sucrose (Radiochemical Centre, >350 mCi mmol⁻¹) per ml. Cells in two other dishes serving as controls were exposed to complete medium only. After 24 h the cell sheets were washed with medium. In dishes with U-¹⁴C-sucrose six washes were sufficient to remove all extracellular radioactivity. Subsequently, control cells were layered with fresh complete media and sucrose-loaded cells with complete media alone (two dishes) or mixed with liposome-entrapped invertase (0.75 mg lipid² and 20–25 units⁵ invertase ml⁻¹, two dishes) or liposome-entrapped heat inactivated invertase (0.70 lipid and 0.6 mg protein ml⁻¹ (ref. 14), two dishes). All dishes were then gassed with 10% CO₂-air mixture and incubated at 37° C. During incubation, the media were assayed for latent invertase activity⁵ and radioactivity¹⁵, when appropriate. Before the addition of liposomes and at intervals thereafter, cells on coverslips were fixed¹¹ with 1.25% glutaraldehyde in 0.2 M sodium cacodylate-HCl buffer, pH 7.4 and examined with the oil immersion phase contrast objectives of the Zeiss Universal microscope. In other experiments macrophages in three dishes were exposed to 10 mg sucrose mixed with 25 μ Ci U-¹⁴C-sucrose ml⁻¹ for 24 h, washed with medium 199 and overlaid with 2 ml complete medium or medium containing liposome-entrapped active or inactive invertase. After incubation for 1 h at 37° C the cells were washed with medium 199 to remove all extracellular invertase and covered with 2 ml complete medium. After 24 h at 37° C, radioactivity released from the cells into the media was assayed and identified chromatographically (see legend to Table 2).

Exposure of macrophages and fibroblasts to sucrose resulted in the appearance of numerous phase-lucent vacuoles in the perinuclear region of virtually all cells examined (Fig. 1b, f). Extensive vacuolation was retained for at least 5 h (macrophages) and 24 h (fibroblasts) after replacement of the sucrose-containing media with sucrose-free media, and apart from being vacuolated, sucrose-loaded cells appeared normal and similar to control cells (Fig. 1a, e). Incubation of sucrose-loaded macrophages (3 h) and fibroblasts (24 h) in media containing invertase entrapped in liposomes led to the disappearance of vacuoles from most of the cells studied (Fig. 1c, g). During incubation more than 96% of the liposomal invertase activity in such media retained its latency for up to 24 h. The latency of invertase activity was the result of the enzyme being surrounded by lipid bilayers rather than being inhibited by the presence of liposomal lipids; addition of invertase-free liposomes into media (0.70 mg lipid ml⁻¹) containing free invertase (20 units ml⁻¹) and incubation for 24 h did not inhibit invertase activity. Exposure of sucrose-loaded cells to inactive invertase-containing liposomes had no effect on the vacuolation of the cells (Fig. 1d, h) and the presence of liposomal lipid in the media (0.70 mg ml⁻¹) did not seem to affect the well-being of the cells (Fig. 1).

The morphological evidence for the elimination of sucrose from sucrose-loaded cells by liposomal invertase was supported by results from experiments with U-¹⁴C-sucrose-loaded macrophages. On incubating these cells with invertase-containing liposomes, much more radioactivity was released in the media than from cells incubated in the presence or absence of liposome-entrapped inactive invertase (Table 1). In addition, released radioactivity was associated with sucrose and its hydrolysis products, glucose and fructose, only in cells previously pulsed with active invertase-containing liposomes (Table 2).

These data suggest that invertase entrapped in liposomes is taken up by the cells by way of liposome uptake, and that it

Fig. 1 Morphological observations on sucrose-loaded cells exposed to invertase-containing liposomes. Monolayers of mouse peritoneal macrophages (*a-d*) and human embryo lung fibroblasts (*e-h*) were incubated in sucrose-free (*a,e*) or sucrose-containing media (*b-d,f-h*, 10 mg sucrose ml⁻¹) for 24 h. Sucrose-loaded cells were then exposed for 3 h (macrophages) or 24 h (fibroblasts) to media mixed with liposomes containing invertase (0.70 mg lipids and 20–25 units invertase ml⁻¹, *c,g*) or heat inactivated invertase (0.75 mg lipids and 0.6 mg protein ml⁻¹, *d,h*) or to media only (*b,f*) (see text). More than 96% of the invertase activity in the media, when present, was latent and it could be measured only after disruption of the lipid bilayers with 'Triton' X-100 (0.1% final concentration). The small amount of "free" invertase in the media (less than 0.8 units ml⁻¹) could not account for the elimination of phase-lucent vacuoles from the cells because in preliminary experiments with free invertase 2.4 units invertase ml⁻¹ medium was inadequate in decreasing vacuolation to any measurable extent in sucrose-loaded cells. Note the disappearance of the perinuclear phase-lucent vacuoles from sucrose-loaded cells treated with active invertase-containing liposomes and their persistence upon treatment with inactive invertase-containing liposomes. Photographs of typical cells shown here were prepared with PAN F 35 mm film (2,300 macrophages; 1,500 fibroblasts).

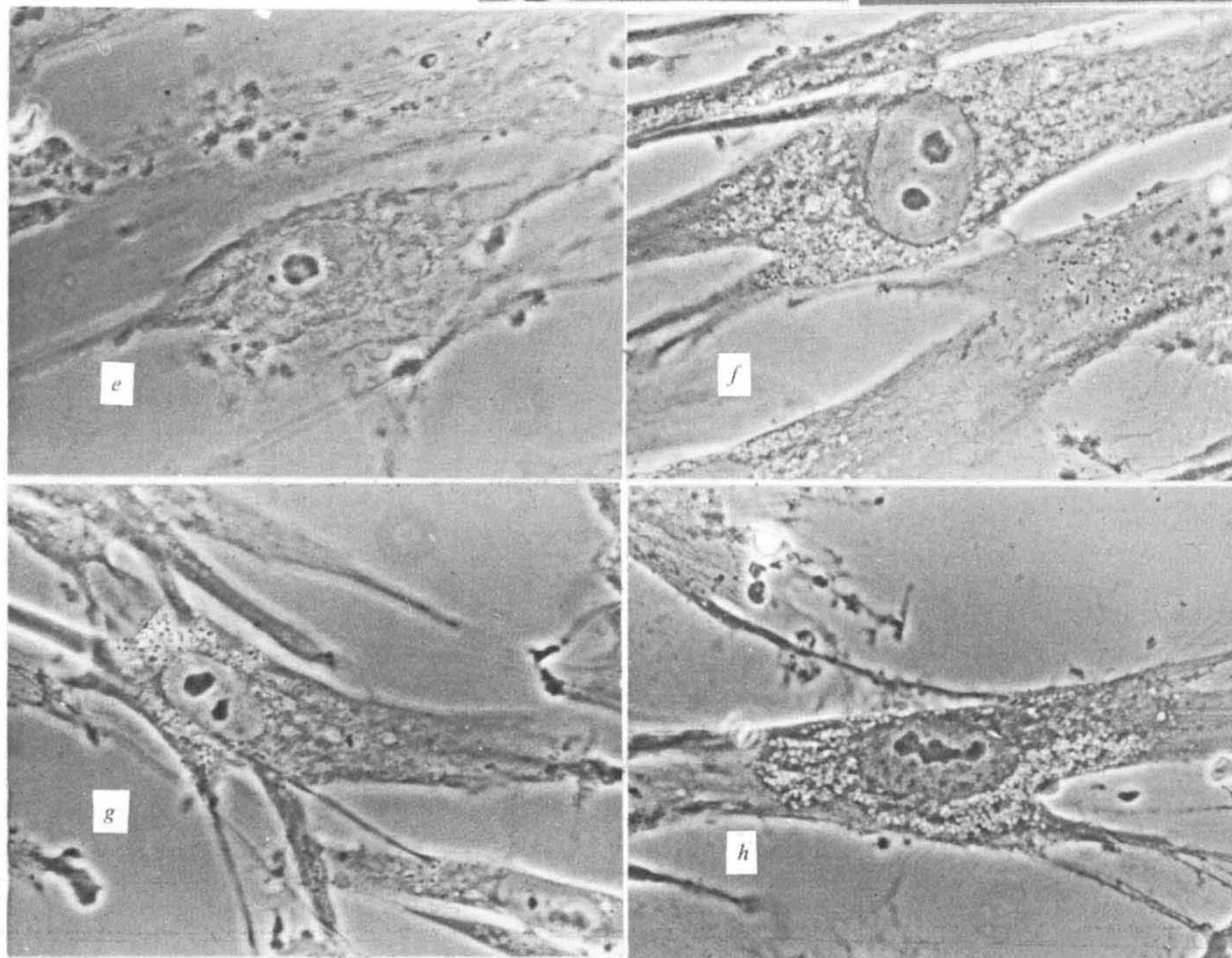
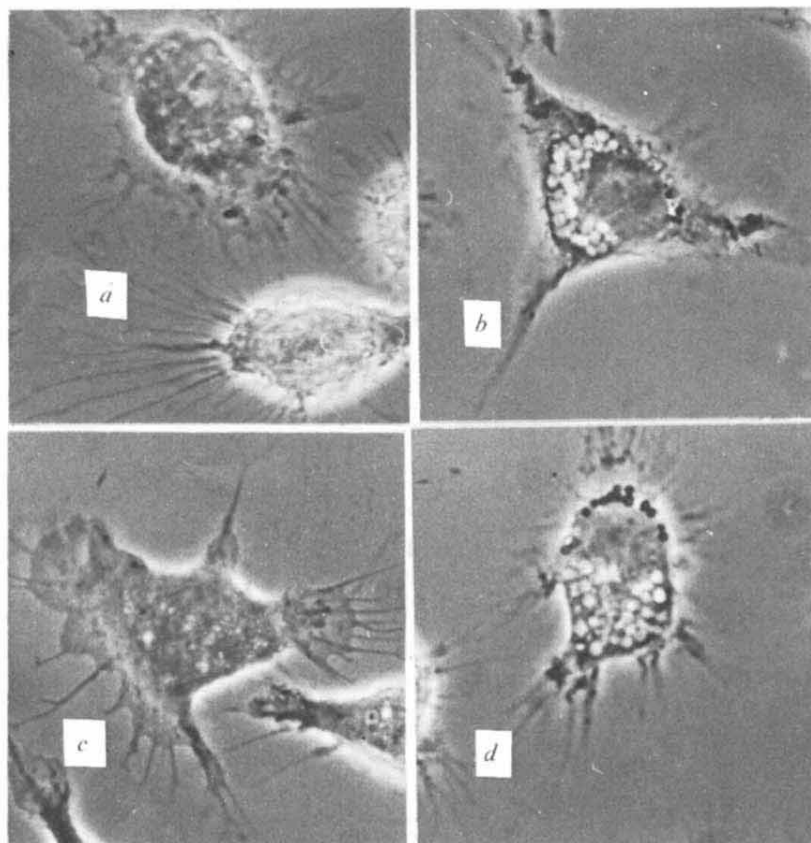


Table 1 Radioactivity Released from U-¹⁴C-Sucrose-loaded Cells after Exposure to Invertase-containing Liposomes

Dish No.	Treatment	Radioactivity released* (%)
1	Liposome-entrapped active invertase	66.1
2	Liposome-entrapped active invertase	78.5
3	Liposome-entrapped active invertase	64.0
4	Liposome-entrapped inactive invertase	26.5
5	Liposome-entrapped inactive invertase	22.2
6	None	19.0
7	None	25.1

Monolayers of mouse peritoneal macrophages ($1.2-2.5 \times 10^6$ cells per dish) were incubated in 4 ml sucrose-containing media (10 mg sucrose and $12.5 \mu\text{Ci}$ U-¹⁴C-sucrose per ml) for 24 h and then exposed to media containing liposome-entrapped active (dishes 1-3) or inactive invertase (dishes 4, 5) or to complete media only (dishes 6, 7) (see text). Three hours later radioactivity, and invertase activity when appropriate, were measured in the media, and radioactivity in the cells after their detachment¹⁷ from the plastic surface. During incubation, more than 96% of the invertase activity in the media (dishes 1-3) was latent.

* Radioactivity released into the media at 3 h as a percentage of total radioactivity ($1.5-2.5 \times 10^4$ d.p.m. per dish).

Table 2 Release of Radioactive Glucose and Fructose from U-¹⁴C-Sucrose-loaded Macrophages Pulsed with Invertase-containing Liposomes

Dish No.	Treatment	Released radioactivity (d.p.m. ml ⁻¹ medium)		
		Sucrose	Glucose	Fructose
1	Liposome-entrapped active invertase	11,253	1,780	1,830
2	Liposome-entrapped inactive invertase	11,850	51	26
3	None	13,600	21	40

Monolayers of mouse peritoneal macrophages (2.5×10^6 cells per dish) were incubated for 24 h in media containing 10 mg sucrose and $25 \mu\text{Ci}$ U-¹⁴C-sucrose ml⁻¹ and then exposed briefly (1 h) to media containing liposome-entrapped active (dish 1) or inactive (dish 2) invertase, or to media only (dish 3). Subsequently, the cells were covered with media and incubated for 24 h (see text). Radioactivity released from the cells into the media was assayed and identified chromatographically: media were freed of protein by the addition of equal volumes of 0.05 M ZnSO₄ and 0.05 M Ba(OH)₂ and centrifugation. The supernatants were freeze-dried and the residues redissolved in 0.4 ml of water containing 0.02% sucrose, glucose and fructose respectively. Descending chromatography of 0.05 ml samples was carried out on a Whatman No. 3 paper with ethyl acetate: pyridine:water (3:1.25:1) as a solvent¹⁸. Following location and identification of sugars with aniline-diphenylamine reagent¹⁹ relevant areas of the paper were cut and extracted with water at 80° C. The extracts were then assayed for radioactivity¹⁵.

eventually finds its way into the sucrose-loaded secondary lysosomes. After disruption of liposomal membranes (perhaps upon the action of lysosomal lipases) entrapped invertase escapes and hydrolyses sucrose to glucose and fructose which then diffuse out to the media¹¹.

In many genetic disorders, well documented enzyme defects are expressed in fibroblasts¹⁶ and it would seem of interest to attempt replacement of missing enzymes in such cells by relevant enzymes entrapped in liposomes. Encouraging results from such experiments would provide further justification for exploring the possibility of using liposomes as vehicles for therapeutic agents in the treatment of some inherited enzyme deficiencies in man.

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GREGORY GREGORIADIS
ROSEMARY A. BUCKLAND

Clinical Research Centre,
Watford Road,
Harrow, Middlesex HA1 3UJ

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Locating Protein in Membranes

I RECENTLY summarized X-ray diffraction data from some natural membranes to show that the original Danielli-Davson model is not valid for them¹. A second widely-discussed structural model, having protein inserted into a lipid bilayer, was put forward as an alternative. I wish to add here that the low angle X-ray diffraction patterns of these membranes show regular changes in proportion to the protein content and that the changes are accounted for by the alternative model.

First, the peak at the origin of the diffraction pattern becomes higher with increasing protein content. Assuming constant partial specific volumes for the lipid and protein¹, the maximum intensity at the origin will increase with the ratio of electron dense protein to the less electron dense lipid in a membrane immersed in water. The maximum intensity will not depend on the arrangement of the constituent molecules. Second, the minimum intensity between the origin peak and the first bilayer band³ moves away from the origin with increasing protein content (Table 1). The outward shift of the first minimum is identified as an effect of inserting protein into the core of the lipid bilayer, where the electron poor lipid fatty chains lie.

Table 1*

Membrane	Lipid: protein (wt:wt)	Distance from origin of diffraction pattern		
		to first minimum, $R_{1/2}$	to first bilayer band, R_1	$R_{1/2}:R_1$
Egg lecithin	100:0	0.004 Å ⁻¹	0.026 Å ⁻¹	0.15
Purple membrane lipids†	100:0	<0.006	0.022	<0.27
Myelin	75:25	0.006‡	0.019‡	0.33
Visual cell disk	40:60	0.008‡	0.023‡	0.36
Purple	25:75	0.013	0.023	0.57

* Addendum to Table 1 in ref. 1. All membranes were immersed in water, except the visual cell disks, which were in the cytoplasm of the visual cell outer segment.

† Unpublished observation of A.E.B.

‡ Measured on the squared Fourier transform calculated from the profile of electron density derived for the single membrane.

Using Fig. 5 from ref. 3, it may be confirmed that the origin peak becomes higher relative to the first bilayer band and that the first minimum shifts outward as the trough in the middle of the bilayer electron density profile becomes shallower.

Moreover, these predictions are not limited to a symmetric profile, although one is aided by the low diffracted intensity found in each case at the first minimum. That part of a protein molecule inserted into either layer of lipid headgroups will cause comparatively little change in the profile, and therefore in the diffraction, because the headgroups are also electron dense. The effect of protein outside the bilayer is treated elsewhere². In Table 1, the purple membrane¹ again provides the most striking evidence for the alternative bilayer structure. For myelin, the first bilayer band is unusually close to the origin. This is partly because of a thicker lipid bilayer¹, and partly because of electron dense material, presumably protein, extending outwards from the bilayer headgroups.

It remains to be decided if the protein molecules penetrate from the surfaces to the centre of the membrane or if each molecule reaches from one surface to the other. The equatorial diffraction from the purple membrane suggests two layers of protein molecules.

In the last paragraph of ref. 1 the first two references are to number 17, not 18.

A. E. BLAUROCK

Medical Research Council,
Biophysics Unit,
King's College,
26-29 Drury Lane,
London WC2

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Emergence of Rifampin-resistance in *Chlamydia trachomatis*

RIFAMPIN exerts marked antibacterial action through the inhibition of DNA-dependent RNA polymerase. Rifampin is used clinically in treatment of tuberculosis, meningococcal carrier states, and some other bacterial infections. In all types of bacteria examined, the incidence of rifampin-resistant mutants was high^{1,2}. Thus the wisdom of using rifampin as the sole drug in a chronic infection where protracted treatment might be required for clinical cure has been questioned.

The chlamydiae causing trachoma, a widespread infectious eye disease, are essentially Gram-negative bacteria (*Chlamydia trachomatis*) which are obligate intracellular parasites because of an ill-defined defect in their energy metabolism³. The topical and systemic use of tetracyclines in chronic trachoma can suppress clinical activity but usually fails to eradicate the chlamydiae⁴. Thus, recurrences of disease activity are common, even after tetracycline therapy, and the damage from such recurrences leads to visual impairment in millions of people.

Becker and Zakay-Rones suggested that two sites on the rifampin molecule might participate in the inhibition of chlamydiae⁵. They attributed the principal activity to the site which binds DNA-dependent RNA polymerase, and a lesser activity to the hydrazone side chain. Becker further suggested⁶ that, because of two separate inhibitory sites, the appearance of chlamydial mutants resistant to rifampin might be extremely rare. It had been proposed that rifampin might be capable of eradicating chlamydiae from chronic infections (rather than just temporarily inhibiting them), because the rifampin binding to the RNA polymerase was believed to be irreversible⁷. The importance of eradication therapy in trachoma would be very great. The rapid emergence of resistant mutants in bacterial in-

fections treated with rifampin, however, raised doubts as to whether such eradication therapy is feasible in chronic chlamydial infections.

To obtain direct evidence on this point, we determined the rapidity and magnitude of rifampin-resistant chlamydial mutants, emerging during egg passage in the laboratory.

Two strains of chlamydiae were employed: (a) TE-55, a "fast" egg-killing strain of chlamydiae, presumably derived from Wang's original Peking trachoma isolate PK-2, but now antigenically related to lymphogranuloma venereum type II⁸, in its ninth passage in this laboratory; and (b) AP-2, a strain isolated in 1960 in this laboratory from an American Indian child with classic trachoma, now in its fourteenth yolk sac passage. Stocks of the two isolates were prepared as previously described⁹ and were stored at -60°C . Bacterial sterility and absence of mycoplasmas were established. Stock solutions of 1 mg ml^{-1} rifampin, 3(4-methylpiperazinyl iminomethyl) rifamycin SV, powder, potency $956\text{ }\mu\text{g ml}^{-1}$ (Dow Chemical Co.) in phosphate-buffered saline (PBS) were held at 37°C for 24 h until the rifampin dissolved, then were filtered (Nalgene $0.45\text{ }\mu\text{m}$ grid), distributed in 1 ml amounts in glass vials, and stored at -20°C .

Freshly thawed stock rifampin was diluted in saline to concentrations of 1 to $400\text{ }\mu\text{g ml}^{-1}$ and added to equal volumes of infected yolk sac suspensions containing about $10^7\text{ ELD}_{50}/\text{ml}$. 0.5 ml was then inoculated into the yolk sac of groups of 7-d embryonated eggs. Eggs were candled daily, and yolk sacs were harvested from all dead embryos and from those surviving 12 d. Impression smears of yolk sac material were stained and examined microscopically for chlamydial infection. Suspensions of heavily infected yolk sacs were transferred to new groups of 7-d embryonated eggs, after mixing with increased amounts of rifampin. After five to seven such transfers, yolk sacs from eggs injected with $200\text{ }\mu\text{g ml}^{-1}$ rifampin were collected, and chlamydial suspensions prepared and frozen. A portion of each such pool was thawed, the ELD_{50} determined, and the absence of bacteria and mycoplasmas ascertained.

Dilutions were made from the drug-treated chlamydial pools and from the original stocks, and each was diluted to result in an average day of death (ADD) of 6 to 8. Each dilution of chlamydiae contained rifampin $200\text{ }\mu\text{g ml}^{-1}$, $20\text{ }\mu\text{g ml}^{-1}$, or none, and each was injected into a group of 7-d embryonated eggs. All eggs were candled daily. Yolk sacs of dead embryos and of those surviving on day 12 were examined microscopically for the presence of specific chlamydial particles. The ADD was calculated for each group from the death dates of microscopically positive embryos. Those surviving on day 12 were considered as dying on day 13.

Rifampin-resistant chlamydiae emerged rapidly during egg passage in the presence of the drug. During the initial exposure of large chlamydial inocula, $5\text{ }\mu\text{g ml}^{-1}$ rifampin prevented death in a majority of embryonated eggs. This inhibitory level of rifampin is comparable with that observed by others^{5,10}. In the course of five to seven passages in embryonated eggs, in the presence of increasing amounts of rifampin, resistant chlamydial mutants were selected. These mutants caused the death of all inoculated embryonated eggs, even in the presence of $200\text{ }\mu\text{g ml}^{-1}$ of rifampin. Table 1 shows a comparison of each original chlamydial pool with the pool of a mutant, selected from each of the two strains after five and seven drug passages respectively. The drug-resistant mutants seemed to grow at a similar rate to that of the original strain, but the resistant mutants reached a peak titre one log lower than that of the original inoculum. The ADD was similar for resistant mutants both with and without rifampin.

Our results indicate that, in two strains of chlamydiae, rifampin-resistant mutants are rapidly selected from large

Table 1 Susceptibility to Rifampin of Two Strains of Chlamydiae and of Their Mutants

Chlamydial strain	Inoculum ELD ₅₀ ml ⁻¹	No drug Deaths/total	ADD†	Rifampin (20 µg ml ⁻¹) Deaths/total	ADD†	Rifampin (200 µg ml ⁻¹) Deaths/total	ADD†
TE-55 original	3,000	24/24	6.2	13/27	10.4	4/17	13.0
TE-55 resistant*	4,000	27/27	6.0	25/25	6.1	28/28	7.4
AP-2 original	50,000	29/29	6.4	1/29	12.8	0/31	13.0
AP-2 resistant †	20,000	31/31	6.8	31/31	6.8	28/28	7.8

* After five passages in eggs in presence of rifampin 5 to 200 µg ml⁻¹ (2.5 to 100 µg per egg).

† After seven passages in eggs in presence of rifampin 5 to 200 µg ml⁻¹ (2.5 to 100 µg per egg).

‡ ADD, average day of death of embryonated eggs.

inocula grown in the presence of increasing concentrations of the drug. Nabli¹⁰ had reported complete inhibition of chlamydial agents in eggs by concentrations of rifampin similar to those used by us. However, Nabli's original inocula were perhaps too small (10³ infective particles per egg) to permit rapid selection of mutants, and repeated passage of chlamydiae in eggs in the presence of rifampin had not been attempted. For one of the strains used by us (TE-55), Becker had suggested that rifampin was lethal rather than inhibitory, and that the appearance of rifampin-resistant mutants might be "extremely rare"⁶. Our results suggest that, on the contrary, chlamydiae resistant to high levels of rifampin emerge quite promptly. Thus, the selection of rifampin-resistant mutants in chlamydial populations is not fundamentally different from that in populations of gram negative bacteria^{1,2}. Recently, Tribby *et al.*¹¹ also found that the effect of rifampin on chlamydial multiplication was inhibitory and reversible, rather than lethal as proposed earlier⁵. In view of these findings, any large scale or long term therapy of a chronic infection like trachoma with rifampin as the sole drug appears undesirable.

Limited clinical trials (C. R. Dawson, personal communication) of rifampin in trachoma have shown no advantage over tetracyclines used in the same trials. These experiences illustrate that the extrapolation of limited results, obtained in a single model system, to the clinical application of drugs in human disease may be unwarranted.

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H. KESHISHYAN
L. HANNA
E. JAWETZ

Department of Microbiology,
University of California Medical Center,
San Francisco, California 94143

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Scrapie-like Antigen(s) in Ageing Tissues

SOME of the morphological changes in the brain which are found both in the light and electron microscopes in the relatively young mouse or rat with scrapie are also present in the normal animal in old age¹. These include enlargement and increased aurophilia of astroglia, presence of amyloid bodies, occurrence of closely orientated tubules within axis cylinders, and the occurrence of intranuclear inclusion bodies². Recently, too, plaques resembling those found in senile brains have been reported in the scrapie mouse (H. Fraser and M. Bruce, demonstration at the Pathological Society of Great Britain and Ireland, July 1972). It would appear that the disease process has brought forward in time many of the features normally found in old age. Similar ageing changes have not, however, been reported in other organs, perhaps because no study has been specifically directed towards them.

Recently it has been found that brain or spleen from a scrapie mouse when injected into a guinea-pig results in a sensitization of the animal's lymphocytes which shows itself as a greater reaction to scrapie mouse brain presented as antigen than to normal mouse brain. This scrapie-normal difference (SND) can indeed be used as a means of rapid diagnosis of scrapie in the mouse³. Experiments have therefore been set up to determine whether the same difference can result from injection of tissues of old mice and humans. Furthermore, since our previous report it has been established that the increased SND we proposed as a rapid means of diagnosing scrapie can also be elicited by the injection of other tissues such as muscle, liver, and kidney from scrapie mice—in other words the new scrapie antigenic properties are not limited to brain and spleen.

Brain, spleen, liver or kidney in the form of 10⁻¹ suspension in saline cleared by centrifugation for 10 min at 1,800g was prepared from mice of different ages and inoculated (0.1 ml intracutaneously: dorsum right foot) into adult Hartley guinea-pigs (500 g: both sexes) and their lymphocytic reactivity to scrapie mouse brain and spleen, compared with normal brain and spleen, estimated after 8 d. The mouse tissues used as inocula came from Webster-Swiss (male) animals between 27 d and 35 months of age. The guinea-pig lymphocytes were tested after 8 d by the macrophage electrophoretic migration (MEM) test described by Field and Caspary^{4,5} of which full operational details together with an experimental protocol *in extenso* are given by Caspary and Field⁶. In principle the method depends upon the observation that when sensitized lymphocytes interact with antigen, a protein is liberated into the ambient medium with the property of causing normal guinea-pig macrophages to travel more slowly in an electric field. Normal macrophages can thus be used as an indicator system for lymphocyte-antigen interaction. If t_e = time of macrophage migration when antigen is present with lymphocytes and macrophages; t_c = control time, that is when no antigen is present; then $t_e > t_c$ and $t_e - t_c / t_c \times 100$ is a measure of lymphocyte sensitization. It is

these percentage slowing figures which are presented in the tables.

Response to scrapie material is always greater than to corresponding normal tissue. The latter indeed remains almost unchanged. The difference between response to scrapie and normal (SND) has been calculated in Table 1 where it is clear that in respect of both brain and spleen it increases with the age of the mouse from which the material was taken for injection into the guinea-pig. Indeed the SND comes into the range observed with tissue derived from a scrapie mouse when the injected tissue is from a normal animal of 28 months. This special antigenic property of old tissue is not limited to the

In a third series of experiments, blood lymphocytes from humans of different ages were tested for reactivity towards scrapie and normal brain and spleen. No age differences were found. This indicates that whilst new antigenic determinant(s), akin or identical with those appearing in the young mouse with scrapie, appear in old tissues, the autologous lymphocytes show no special sensitization to them. This does not mean, however, that the antigenic properties of the lymphocytes themselves (when injected into guinea-pigs) are not affected by age. Old lymphocytes in fact have the same antigens as do old tissues in general (see below). An analogous situation has been observed with respect to leukaemic lymphocytes which,

Table 1 Mouse Ageing

Age (d)		Scrapie brain	Normal brain	Scrapie spleen	Normal spleen	Brain	SND	Spleen
A	Brain injected							
	27	10.4	9.4	5.2	4.0	1.0		1.2
	42	9.1	7.9	6.0	4.7	1.2		1.3
	180	12.1	9.9	6.2	4.0	2.2		2.2
	203	12.4	9.9	7.0	4.4	2.5		2.6
	575	13.2	9.4	9.4	4.4	3.8		5.0
	850	13.8	9.7	9.1	4.3	4.1		4.8
	1,065	14.1	9.3	8.7	4.3	4.8		4.4
B	Spleen injected							
	27	5.0	3.8	10.1	8.9	1.2		1.2
	203	6.8	4.3	11.8	9.2	2.5		2.6
	575	9.1	4.1	13.6	9.1	5.0		4.5
	850	9.0	4.2	12.8	8.8	4.8		4.0
	880	9.2	4.2	14.1	9.4	5.0		4.7
	1,065	7.6	2.8	13.2	9.6	4.8		3.6
C	Liver injected							
	27	5.5	4.4	5.4	4.4	1.1		1.0
	203	6.9	4.4	6.7	4.4	2.5		2.3
	575	7.6	3.9	7.2	3.2	3.7		4.0
	850	7.9	3.9	7.5	2.9	4.0		4.6
	880	9.2	4.3	9.7	4.4	4.9		5.3
D	Kidney injected							
	27	5.3	4.4	5.2	4.2	0.9		1.0
	203	7.0	4.6	6.9	4.3	2.4		2.6
	575	7.7	4.0	7.0	3.4	3.7		3.6
	850	8.0	4.4	7.7	3.7	3.6		4.0

Fresh mouse tissues (0.1 ml: 10^{-1}) injected into guinea-pigs and lymphocyte sensitization measured after 8 d.

nervous system. Liver and kidney also showed these antigenic properties as the animal became older.

In a second series of experiments formalin fixed human brain, spleen, heart, liver and kidney suspensions were made (10^{-1} in saline after washing out the formalin) from subjects of different ages ranging from 20 to 91 (supplied by Dr J. N. Corsellis). All were female. The causes of death were: age 20: cerebral and subarachnoid haemorrhage associated with an arterio-venous malformation of the brain; age 30: bronchopneumonia and encephalitis; age 52: fracture of base of skull leading to carotid-cavernous fistula; age 72: perforated duodenal ulcer with generalized peritonitis; age 91: femoral vein thrombosis embolism.

All patients died from acute disease and none had suffered from chronic disease. In each case 0.1 ml of the 10^{-1} suspension cleared by centrifugation at 1,800g for 10 min was injected intracutaneously on the dorsum of the right foot of Hartley guinea-pigs. Lymphocyte sensitization was measured as in the previous experiments.

It is apparent from Table 2 that SND increases with age for all the human tissues studied just as in the ageing mouse. Here, too, the increase is largely due to the greater response to scrapie tissue antigen when guinea-pigs have been injected with older material. The occurrence of greater SND with ageing is thus shared by mice and humans.

whilst unable to react with encephalitogenic factor⁴ or cancer basic protein, nevertheless possess cancer basic protein determinant(s) on their surface⁷. It is interesting that only a minor (but significant) rise in lymphocyte sensitization to encephalitogenic factor (EF) and cancer basic protein (CaBP) has been found to occur with ageing⁸. The new determinant(s) arising in old tissues are thus regarded as "self" but are recognized as different from those present in young tissues when presented to guinea-pigs.

It was of interest to find out if the new antigen(s) resembling scrapie antigen might be present in (or on) old lymphocytes. Accordingly 10^7 cells prepared from a normal girl of 16 and from an old lady of 91 (normal) were injected into guinea-pigs and found to produce SNDs of 0.9 (brain) and 0.7 (spleen) for the young person; and 6.2 and 5.8 for the old. Thus lymphocytes, too, exhibit the same antigenic changes as other old tissues so that a specimen of these cells offers a convenient "biopsy" in assessing ageing or for research purposes.

Finally, because it is generally thought that thymectomy in the neonatal mouse accelerates its clinical ageing, a short series of experiments has been carried out to determine whether scrapie-like antigenicity appears precociously in the tissues of the young mouse thymectomized at birth compared with a normal or sham operated animal. It is clear from Table 3 that following neonatal thymectomy antigen(s) of the scrapie-old

Table 2 Human Ageing

		Antigen				SND		
		Scrapie brain	Normal brain	Scrapie spleen	Normal spleen	Brain	Spleen	
A	Age (yr)							
	Brain injected							
	F, 20	10.8	9.7	5.4	4.5	1.1	0.9	
	F, 30	10.3	9.3	5.3	3.9	1.0	1.4	
	F, 52	12.9	9.1	9.4	5.8	3.8	3.6	
	F, 72	14.3	9.6	11.1	5.7	4.7	5.4	
B	F, 91	13.5	9.2	10.9	6.0	4.3	4.9	
	Spleen injected							
	F, 30	5.3	4.3	10.4	9.8	1.0	0.6	
	F, 91	10.5	3.9	14.8	9.3	6.6	5.5	
	C	Heart muscle injected						
		F, 30	5.1	4.3	5.2	4.3	0.8	0.9
F, 91		9.0	4.2	8.4	4.1	4.8	4.3	
D	Liver injected							
	F, 30	5.1	4.3	5.0	4.0	0.8	1.0	
	F, 91	10.2	4.5	10.3	4.4	5.7	5.9	
E	Kidney injected							
	F, 30	5.2	4.2	5.0	4.2	1.0	0.8	
	F, 91	8.8	3.5	9.1	4.4	5.3	4.7	

Formalin fixed human brain, spleen, heart, liver and kidney injected into guinea-pigs (0.1 ml: 10^{-1}) and lymphocyte sensitization measured after 8 d.

Table 3 Effect of Thymectomy on SND

	Antigen				SND	
	Scrapie brain	Normal brain	Scrapie spleen	Normal spleen	Brain	Spleen
(a) Brain injected						
Thymectomized	12.6	9.3	8.0	4.2	3.3	3.8
Sham (normal)	9.6	8.3	6.1	4.9	1.3	1.2
(b) Spleen injected						
Thymectomized	8.5	4.2	13.2	9.2	4.3	4.0
Sham (control)	—	—	—	—	—	—

Neonatally thymectomized animal aged 39 d: brain and spleen injected into guinea-pigs: lymphocyte sensitization measured after 8 d.

age type rapidly appear so that SND of the order ordinarily given by the normal mouse of about 12 months is found in an animal with a calendar age of only 39 d. Neonatal thymectomy has an extensively documented effect on the development of the lymphatic system, and immunological processes have been thought to be involved in the mechanism of ageing⁹⁻¹². Recently¹³ Fabris *et al.* have examined the possible importance of the thymus as a biological clock and of hormones for the ageing processes of the lymphoid system. They found thymus dependent cells important in preventing early ageing, a conclusion consistent with that from our own recent work. Different strains of mice show considerable variation in ageing changes¹⁴, so it would be of interest to study the dependence of SND upon the various factors considered by Simms¹⁵ as affecting the ageing process.

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E. J. FIELD*
B. K. SHENTON

Medical Research Council,
Demyelinating Diseases Unit,
Newcastle General Hospital,
Westgate Road,
Newcastle upon Tyne NE4 6BE

Received January 23, 1973.

* Present address: Institute of Pathology, Newcastle General Hospital.

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Malignant Tumours of Liver and Lung in Rats fed Aminopyrine or Heptamethyleneimine together with Nitrite

SOME human cancer might be caused by nitrosamines formed in the gastrointestinal tract from nitrite in the food and secondary or tertiary amines ingested deliberately or incidentally¹⁻³. This hypothesis was supported by experiments in which rats fed with nitrite and secondary amines developed the same type of tumours as after treatment with the respective nitrosamines⁴.

Table 1 Tumour Incidence in Sprague-Dawley Rats fed Amines and Nitrite Concurrently in Drinking Water

Amine and nitrite concentration (p.p.m.)	Treatment duration (weeks)	No. of animals	Average dose per animal (mg per week)	Tumour-bearing animals per animals dead	No. with primary tumours of*			
					Liver	Lung	Oesophagus	Other
Aminopyrine (1,000)	30	15 ♂	53	14/15	14	0	0	0
		15 ♀	40	15/15	15	1	0	1
Aminopyrine (250)	50	15 ♂	20	4/4	4	0	0	0
		15 ♀	20	9/10	8	0	0	3
Heptamethyleneimine hydrochloride (2,000)	28	15 ♂	156	6/8	0	2	3	4
		15 ♀	140	14/15	0	11	14	4

* One of the twelve animals with a liver tumour also had a parotid tumour.

The reaction in the stomach of the secondary amine heptamethyleneimine with nitrite to form its *N*-nitroso derivative, nitrosoheptamethyleneimine, could serve as a model for lung cancer induction in man. Nitrosoheptamethyleneimine is a potent respiratory tract carcinogen when given orally to rats^{5,6}. An earlier rat feeding test, using heptamethyleneimine with nitrite at low doses failed to elicit any lung tumours (H. Garcia and W. L., unpublished observations), possibly because the free amine, which is a strong base, was used. In the present experiments the amine was administered as the neutral hydrochloride.

Formation of nitrosamines by reaction of tertiary amines with nitrite in mildly acidic conditions seems to be a general phenomenon⁷, and some tertiary amines widely used as drugs form nitrosamines with nitrous acid⁸. Among these is the analgesic aminopyrine (pyramidon), which reacts with nitrite in acid solution to form large amounts of dimethylnitrosamine, and which was lethal to rats when given simultaneously with nitrite in a single intragastric treatment⁸. We carried out a long-term feeding study using nitrite and aminopyrine (a drug that has been widely used, sometimes chronically), to discover whether such a combination represents a potential carcinogenic hazard to man.

A solution containing amine and nitrite was given as drinking water: heptamethyleneimine hydrochloride, 2 g l⁻¹ + sodium nitrite, 2 g l⁻¹; aminopyrine, 1 g l⁻¹ + sodium nitrite, 1 g l⁻¹; and aminopyrine, 250 mg l⁻¹ + sodium nitrite, 250 mg l⁻¹. Each test group comprised fifteen male and fifteen female Sprague-Dawley rats, housed three to a cage. Each cage of rats was offered 60 ml of solution 5 days a week, and the volume left each day was measured, so that average consumption of the compounds could be calculated; the animals received tap water at weekends. The control groups of thirty rats were each given 1 g l⁻¹ of aminopyrine, 2 g l⁻¹ of heptamethyleneimine hydrochloride, or 2 g l⁻¹ of sodium nitrite. The heptamethyleneimine + nitrite solutions were prepared weekly and the aminopyrine + nitrite solutions were prepared daily (aminopyrine solutions decompose slowly in light). The pH of all solutions was close to neutrality (6.8–7.2), and gas chromatographic analysis of methylene chloride extracts of the solutions that contained the amine + nitrite, after standing more than one week in the dark, showed that only minute amounts of the nitrosamines had been formed (<0.1% theoretical).

The animals were fed heptamethyleneimine hydrochloride solutions for 28 weeks, aminopyrine + nitrite (1 g l⁻¹) for 30 weeks, and the lower dose of aminopyrine + nitrite for 50 weeks. The animals were observed until death, and complete post-mortem and histopathological examinations were performed.

None of the controls fed nitrite, aminopyrine, or heptamethyleneimine alone died, with the exception of one accidental death and one animal that died with a large mammary tumour. The tumour incidence data are summarized in Table 1. Of the thirty animals fed aminopyrine + nitrite (1 g l⁻¹), all died within one year of treatment, twenty-nine with haemangioendothelial

sarcomas of the liver. These tumours were highly malignant, metastases of the lung occurring in seventeen of the test animals. Of the thirty animals receiving the lower dose of aminopyrine + nitrite, fourteen died within the first year, twelve with liver tumours similar to those seen in the animals on the high dose, one with a parotid tumour, and one with a large mammary tumour. Metastases of the lung occurred in six animals with tumours. Other authors report⁹ that dimethylnitrosamine, a product of the nitrosation of aminopyrine, causes haemorrhagic liver tumours in rats.

In the group fed heptamethyleneimine + nitrite, twenty-three of the thirty animals died in the first year of treatment. Twenty animals developed primary tumours in one or more sites. Most prevalent were oesophageal papillomas (seventeen animals) and squamous cell carcinoma of the lung (thirteen animals), but other sites included nasal turbinates, pharynx, tongue and trachea. Squamous cell carcinomas metastasized to the kidney in two animals. Tumours of the lung and oesophagus are commonly induced in these rats by nitrosoheptamethyleneimine⁶.

The results of these experiments suggest that the interaction of secondary and tertiary amines with nitrite in the stomach may represent an important facet of the aetiology of cancer in man. The doses used do not greatly exceed those encountered in human experience (the permitted limit of nitrite in food in the USA is 200 p.p.m.), yet a high tumour incidence was observed after 28 to 50 weeks of treatment, as a result of nitrosamine formation.

Other amines to which man is exposed react less readily with nitrite than does aminopyrine, and they would usually be present in smaller amounts than those used here. Therefore, daily exposure of man to nitrosamine formed in this way would be lower than in our experimental animals. Man's exposure could, however, be continuous over several decades and therefore quite significant. The incidence of cancer in man is quite large, and the distribution of cancers of certain types in sections of the population seems to reflect well-defined exposures to carcinogenic agents. Part of the explanation for these patterns might lie in the reaction of nitrites with amines, because individual intakes of one or the other might vary considerably, and the amount of nitrosamine formed depends on the amounts of amine and nitrite present.

The occurrence of a high incidence of squamous lung tumours in rats fed the amine heptamethyleneimine together with nitrite suggests that a significant source of the lung cancer found in large numbers of cigarette smokers might be carcinogenic nitrosamines, formed from nitrite in the food and secondary or tertiary amines in cigarette smoke condensed in the mouth and swallowed in the saliva. That many very heavy smokers do not develop lung cancer might be explained on this basis by their relatively low intake of nitrite.

The readiness with which aminopyrine reacts with nitrite, even at quite low concentrations, to form dimethylnitrosamine suggests that taking this drug concurrently with food containing

nitrite may represent a very significant carcinogenic hazard. Present incidences of some human cancers might reflect past intake of aminopyrine, the use of which has only recently stopped in some countries (including the USA) but is still continued in other parts of the world. As many other drugs react with nitrous acid to form nitrosamines, measurably though less readily than aminopyrine, there is need for further studies of the formation of nitrosamines *in vivo* from nitrite and amines. Our findings give urgency to the need for reduction of the residual nitrite in food to the minimum and for elimination from food of nitrite when it is not needed for health reasons.

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W. LIJINSKY
H. W. TAYLOR
C. SNYDER
P. NETTESHEIM

Carcinogenesis Program, Biology Division,
Oak Ridge National Laboratory,
Oak Ridge, Tennessee 37830

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Role of Activity in the Differentiation of Slow and Fast Muscles

If adult skeletal muscles are denervated the difference in twitch speed between slow and fast muscle persists^{1,2}. This suggests that either there are inherent differences between the two types of muscle or that, once differentiated, they can only alter their contractile properties if another pattern of activity is imposed on them by cross-union of slow and fast motor nerves³ or by stimulation⁴. The finding that there is a difference in contractile properties already at birth⁵ suggests that slow and fast muscles have inherent differences. These experiments were performed to see whether slow and fast muscles can differentiate from birth in the absence of innervation.

Unilateral section of the sciatic nerve was carried out in rats under ether anaesthesia within twelve hours of birth. One to six weeks later, soleus and extensor digitorum longus (EDL) muscles were removed from both legs and set up for tension recording as described by Blunt and Jones⁶. Time to peak contraction was measured from single twitches at 19–20°C in response to direct supramaximal stimulation.

It was found that the contraction speeds of soleus and EDL are already differentiated at birth, as reported by Close⁵. The speeds of both muscles increase most rapidly during the first three weeks of life, after which there is little change. These developmental changes in the time course of contraction of soleus and EDL occur in parallel (Fig. 1a). When the muscles were denervated at birth, the contraction times of soleus and EDL became very similar. This was because the time course of contraction of the fast EDL changed very little although the speed of contraction of the denervated soleus increased during development (Fig. 1b). Similar results were obtained in rabbits but the time course of these changes is faster, in that the most rapid increase in speed of the muscles occurs during the first one to two weeks after birth.

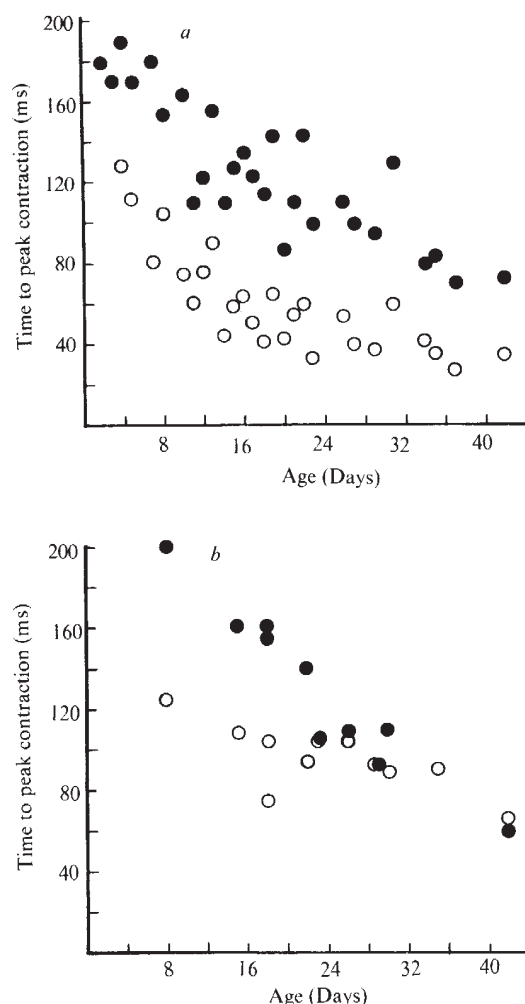


Fig. 1 Development of contraction times for slow soleus (●) and fast EDL (○) rat muscles with age. a, Normal development; b, development after denervation at birth.

Thus, while both muscles possess the potential to increase their contraction speeds in the absence of innervation, EDL is dependent on neural influences for the completion of this process. These results are in accord with histochemical and morphological studies which show a differential response of slow and fast muscle fibres to denervation at birth. Potential fast fibres fail to mature, while slow fibres can develop without innervation⁷.

It may be that the activity of the muscle itself is important in maintaining the functional integrity of the contractile mechanism. When a muscle becomes inactive, the fibres atrophy and there are changes in the contractile properties, whether the inactivity is produced by denervation⁸, tenotomy⁹, immobilization¹⁰, or de-afferentation and spinal cord section¹¹. Further experiments were therefore performed to study whether activity plays a role in the development of the contractile properties of fast muscles.

Rabbits were used for these experiments as the developmental changes in contraction times are similar to those in the rat, and the larger size of the animals is more suitable for the implantation techniques used. Pairs of rabbits from the same litter were anaesthetized at birth and the sciatic nerve was cut on one side. Two to four weeks later, electrodes were implanted into the denervated leg of one rabbit using the technique described by Pette *et al.*¹². The electrodes were arranged to stimulate the tibialis anterior and EDL muscles directly. The denervated muscles were stimulated for 6–8 h daily, in 2 h sessions, for 4–8 d. In between each 2 h period of stimulation, the baby rabbit was returned to the mother

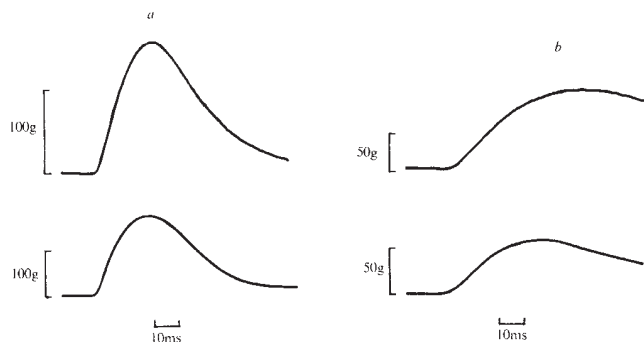


Fig. 2 Single twitches from rabbit tibialis anterior muscles. *a*, Control and denervated muscles from one rabbit. (Contraction times: control, 25 ms; denervated, 61 ms.) *b*, Muscles from a littermate in which the denervated muscle had been stimulated for 7 d at a frequency of 10 s^{-1} . (Contraction times: control, 23 ms; denervated, 41 ms.)

for feeding and rest. Trains of pulses lasting 500 ms were given every 2 min at a frequency of $10\text{--}40\text{ s}^{-1}$ and pulse duration of 0.5 ms. The voltage was adjusted to give a barely visible contraction of the muscles.

In the final experiments, the rabbits were anaesthetized and their EDL and tibialis anterior muscles dissected and prepared for tension recording⁴. Control muscles were stimulated through the cut motor nerve and denervated muscles were stimulated directly.

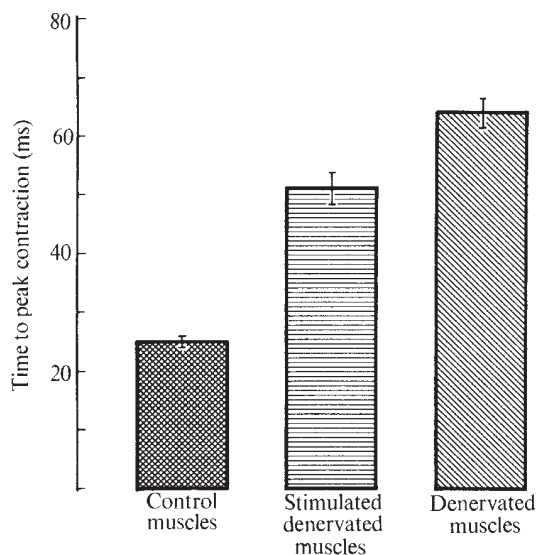


Fig. 3 Means and s.e. for contraction times of tibialis anterior and extensor digitorum longus muscles of young rabbits.

Figure 2 shows examples of single twitches from control, denervated and stimulated denervated tibialis anterior muscles. The stimulated denervated muscle has a faster time to peak than the denervated muscle. This was the case with each pair of littermates for both fast muscles examined. Figure 3 shows mean contraction times of control, denervated and stimulated denervated muscles from ten rabbits.

By replacing some of the activity, of which it has been deprived by severance of its nervous connexions, to a developing fast muscle its contractile properties can be altered so that it appears more like a normal muscle. Thus, the inability of denervated fast muscle to differentiate may, in part, be due to the lack of activity that follows denervation.

M. D. BROWN

Department of Physiology,
University of Birmingham,
The Medical School,
Birmingham B15 2TJ

Received January 3, 1973.

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Selective Grazing and Differential Digestion of Algae by Zooplankton

THE success of future water quality standards and management programmes depends on an accurate assessment of factors determining the relative abundances of algal species. Physical and chemical factors are often considered¹; biological controls are less commonly assessed although their potential importance is recognized²⁻⁴. Planktonic crustacea exhibit selective feeding behaviour ranging from passive size selection in *Daphnia*⁵ to raptorial feeding in cyclopoid copepods⁶. Some algae are actively rejected^{7,8} and others are poorly digested⁹⁻¹¹ by grazers.

To determine the effect of differential grazing on a natural phytoplankton community, I conducted twelve *in situ* experiments during the ice-free months of 1971-72 in Fuller Pond, Kent, Connecticut, an 18 m deep, 17 ha, mesotrophic kettle lake. On each date, three levels of grazing pressure were created inside large, $\approx 0.5\text{ m}^3$ polyethylene bags¹². One bag contained lake water with its natural complement of grazers; a second contained water filtered through 125 μm netting which removed large grazers; a third contained water enriched with grazers from vertical net hauls. The magnitude of enrichment ranged from two to seventeen and averaged eight times the natural zooplankton concentration. The bags were sealed, suspended at 2 m, incubated for 4 d, raised and sampled. Algae were counted by species with an inverted microscope¹³. Large species were defined as those easily counted at low power ($\times 125$) and were generally 20 to 30 μm or more in longest dimension. Small species were those counted at high power ($\times 500$), generally 2-30 μm . Both classes contained algae used by the grazers (up to 40 μm for *D. galeata*⁵). Gut analyses of the filter feeding herbivores *D. galeata mendotae* and *Diaptomus minutus*, raptorially feeding *Cyclops scutifer*, and the carnivore *Epischura lacustris* accompanied each experiment.

Results for species and major size and taxonomic groupings were analysed with a conservative nonparametric Friedman rank test (Table 1). Groups are said to be suppressed by grazers when their numbers are lowest in the zooplankton enriched bags and highest in filtered bags. They are reported as increased by grazers when their numbers are highest in the zooplankton enriched bags and lowest in the filtered bags. When no significant difference is found, groups are reported as unaffected. These experiments represent general effects that hold throughout the year.

All the phytoplankton and ciliates were suppressed in the presence of grazers. The major effect of grazing was suppression of small algae, primarily flagellates and nanoplankton, and large diatoms. Large green algae were increased. Desmids, dinoflagellates and chrysophytes were unaffected. Large blue-greens showed high variability because of clumping, filtration and grazing.

Gut analyses revealed that unaffected groups were dominated by species rarely or never found in the guts of the zooplankton. These include the desmid *Cosmarium depressum*, dinoflagellate *Peridinium willei*, chrysophyte *Mallomonas caudata*, and the filamentous blue-greens *Anabaena affinis* and *A. flos-aquae*, all of which are large (>40 μm) species. When a group is suppressed, it is dominated by species found digested in the gut contents. Easily digested species appear as dispersed cytoplasm and empty husks, and include the flagellates, *Cryptomonas*, *Rhodomonas*, euglenids, the diatoms *Cyclotella comta* and *Asterionella formosa*, and the nondominant, nongelatinous greens *Oocystis lacustris* and unicellular *Chlamydomonas*.

By their responses to grazing, algae can be divided into three major groupings that cut across taxonomic lines. One contains species that are large, rare or filamentous and seldom found in the guts of the zooplankton, either because they are not eaten or are actively rejected. These are unaffected by manipulations of grazing pressure. The second contains small, edible species that are eaten, digested and suppressed by grazers. The third contains species encased in thick, gelatinous sheaths that pass through the grazers, frequently intact and in viable condition. These are increased by an increase in grazers. Grazing pressure, like physical and chemical factors, may determine the relative proportions of algal species and drive seasonal succession from

Table 1 Effect of Experimental Manipulation of Grazing Pressure on the Numbers of Algae and Ciliates

Major groupings	Counting size (classes)	Sums of ranks under experimental manipulations of zooplankton*			Friedman χ^2	P	Response to increased grazing
		Filtered	Unfiltered	Enriched			
Ciliates	Large	35.0	25.0	12.0	22.167	<0.001	Suppressed
Total phytoplankton		35.0	24.0	13.0	20.167	<0.001	Suppressed
Small algal species	Small	35.0	24.0	13.0	20.167	<0.001	Suppressed
Large algal species	Large	25.0	26.0	21.0	1.167		Unaffected
Blue-green algae (Cyanophyta)	Large	24.0	31.0	17.0	8.167	0.02	Variable
	Small	26.0	28.0	18.0	4.667		Unaffected
Green algae (Chlorophyceae)	Large	15.0	26.0	31.0	11.167	0.006	Increased
	Small	25.0	22.0	25.0	0.500		Unaffected
Diatoms (Bacillariophyceae)	Large	28.0	28.0	16.0	8.000	0.02	Suppressed
	Small	26.0	27.0	19.0	3.167		Unaffected
Desmids (Desmidiaceae)	Large	21.0	29.5	21.5	3.792		Unaffected
Dinoflagellates (Dinophyceae)	Large	27.0	27.0	18.0	4.500		Unaffected
Chrysophytes (Chrysophyceae)	Large	29.0	22.5	20.5	3.292		Unaffected
Flagellates and nannoplankton†	Large	36.0	23.0	13.0	22.167	<0.001	Suppressed
	Small	36.0	24.0	12.0	24.000	<0.001	Suppressed

* Each experimental date was considered a block in a randomized block design. Abundances of groups in filtered, unfiltered and zooplankton enriched bags were assigned ranks 1, 2, or 3 according to magnitude. Ranks were summed by treatment over the twelve dates and used to compute a Friedman χ^2 with a critical value of 6.167 ($P < 0.05$).

† Cryptophyceae, Euglenaceae, and unidentifiable flagellates and cells of < 5 μm .

The group increased by the presence of grazers is dominated by green algae encased in thick gelatinous sheaths. These are found intact in the guts and faeces. To determine algal viability, gut contents of live *D. galeata* collected in the lake were cultured. The animals were washed to remove surface contamination and allowed to evacuate their guts in suitable culture medium. Colonies of gelatinous greens (*Sphaerocystis schroeteri* and *Elakatothrix gelatinosa*) reproduced after gut passage. The coccoid blue-green *Chroococcus limneticus* (sheath thin or absent) was sometimes found intact but could not be cultured; it was suppressed by grazers.

The gelatinous green algae are spared from grazing pressure by frequent viable gut passage and can increase while small competitors are suppressed and larger, slower reproducing species cannot respond rapidly. Gelatinous greens may be further encouraged when large colonies are fragmented by *Daphnia* gut passage. This increases their absorptive surface area in contact with lake water. The possibility that they pick up nutrients from broken cells in the gut, their mucopolysaccharide sheaths acting as molecular sieves, allowing small molecular and ionic nutrients to enter while keeping out large digestive enzymes, is also being studied. They are found growing profusely from copepod faecal pellets in the lake. Gelatinous greens must, therefore, be regarded with filamentous blue-greens and very large species as being poorly incorporated in planktonic food chains.

a spring association dominated by edible flagellates and diatoms to gelatinous greens and filamentous blue-greens in autumn. The impact of grazing on the phytoplankton community is determined by the proportions of suppressed, increased and unaffected algae present (my results, in preparation).

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KAREN G. PORTER

Osborn Memorial Laboratories,
Yale University,
New Haven, Connecticut 06520

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Anatomical Evidence for a Counter-current Heat Exchanger in the Leatherback Turtle (*Dermochelys coriacea*)

FRAIR *et al.*¹ have recently given strong circumstantial evidence that leatherback turtles (*Dermochelys coriacea*) can maintain a deep body temperature at least 18° C higher than the ambient temperature of cold water. The mechanisms underlying this differential are largely unknown but are presumed to be muscular activity combined with the thermal inertia of a large body mass and an insulating layer of subepidermal fat¹. Countercurrent flows have also been suspected as a heat retention mechanism¹⁻³ but so far have not been proved. We now present anatomical evidence for a countercurrent heat exchanger in the front and rear flippers of a leatherback turtle, which is the first evidence for this kind of heat retention mechanism in a reptile.

The countercurrent system was discovered during a general dissection of a female leatherback (in preparation) that had recently died in the New England Aquarium after being in captivity for approximately 6 days. The specimen had been captured by Mr Charles Stowe, jun., in 12 fathom of water off Matinicus in the Gulf of Maine on July 28, 1972. Three days after capture the specimen was transported to the aquarium but, as is usual with these turtles, it fared poorly in captivity; plans had been made to release it on the day it died. The specimen weighed 625 pound (284 kg) and had a straight line carapace length of 54 inch (137 cm). Before dissection the turtle had been in the New England Aquarium freezer at approximately -15.5° C for 30 d.

The countercurrent heat exchanger consists of a single well-defined bundle of closely packed veins and arteries which we intercepted near the junction with the body in each of the front and rear flippers. The bundles tend to be deeper than broad and can be readily separated from the surrounding muscle. In the front flipper the bundle ran just posterior and ventral to the humerus and measured approximately 35 × 20 mm at the distal end of the humerus; in the rear flipper the bundle ran just dorsal to the femur and was smaller, measuring 25 × 13 mm at the proximal end of the femur. In gross cross section the veins had collapsed and were difficult to see; the arteries, however, stood out clearly and all seemed to be approximately the same size.

We prepared histological sections from excised pieces of the bundles in all four appendages (Figs 1 and 2) and counted the veins and arteries in each section; the ratio of veins to arteries

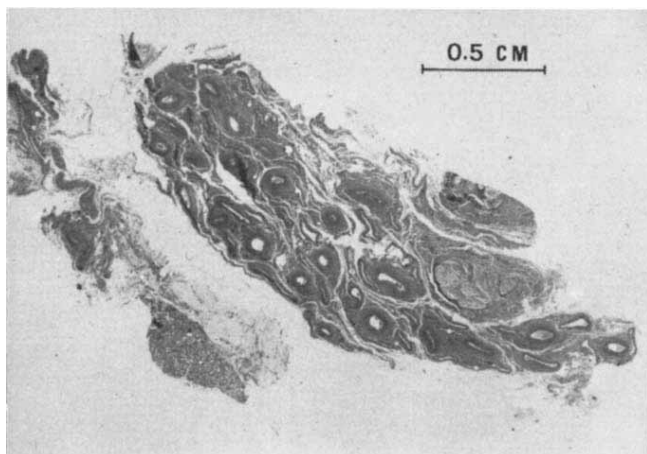


Fig. 1 Cross-section of the vascular bundle in the left rear flipper at the level of the proximal end of the femur. The veins have collapsed but the arteries have maintained their shape.

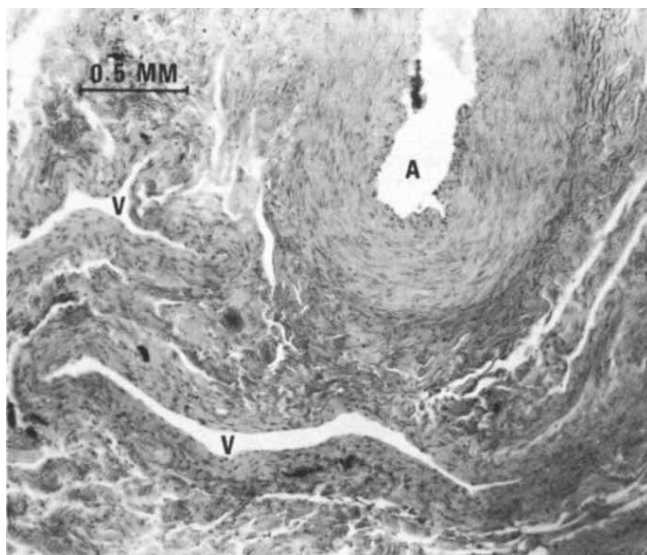


Fig. 2 Detailed view of an artery (A) and two veins (V) in a histological cross-section of the vascular bundle in the left rear flipper at the level of the proximal end of the femur.

in the sections varied from 1.75:1 to 4.2:1 (average = 2.7:1) with no significant difference (χ^2 , $P > 0.05$) between the ratios of any two sections. The maximum number of veins and arteries counted in a complete cross-section from a bundle in the front (right) flipper was seventy-eight and twenty-six respectively and the maximum number for a similar section in the rear (left) flipper was forty-eight and nineteen. These figures probably very nearly represent the complete complement of veins and arteries in the bundles at the base of the respective flippers. In the histological sections veins and arteries seemed to be scattered more or less randomly, and there was no evidence of any unit structure to the veins and arteries within the bundles.

Our knowledge of leatherback turtles now shows that they, of all the reptiles, are the most similar to the homeothermous birds and mammals in their thermal biology: not only can they generate a striking temperature differential between their body core and the external environment in the absence of an external heat source¹, but they have, uniquely for reptiles, the two classic adaptations of birds and mammals for retaining body heat, namely, an insulating layer of subepidermal fat and a countercurrent heat exchanger.

We thank L. B. Garibaldi of the New England Aquarium for making the turtle available and A. F. Bennett, P. K. Greer, R. Huey, C. R. Taylor, P. E. Vanzolini and E. E. Williams for critical reading of the manuscript.

ALLEN E. GREER, JUN.

*Museum of Comparative Zoology,
Harvard University,
Cambridge,
Massachusetts 02138*

JAMES D. LAZELL, JUN.

*Massachusetts Audubon Society,
Lincoln,
Massachusetts 01773*

RICHARD M. WRIGHT

*Department of Biology,
Boston University,
2 Cummington Street,
Boston,
Massachusetts 02215*

Received March 9, 1973.

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Amino Acid Components in Fossil Tortoiseshell from the Oligocene of the Isle of Wight

Fossil bones and teeth from Palaeozoic, Mesozoic and Tertiary rocks have yielded amino acid analyses which indicate the survival of collagenous material over hundreds of millions of years¹. In contrast, fossil keratinous tissues have until now only been recorded in such Pleistocene animals as the South American giant ground sloth and the woolly mammoth². We are not aware of any earlier records. Ostrom³ in his account of the Dutch *Archaeopteryx* noted that "the actual horny claws are preserved", but he has since written that he "did not claim that the original keratin or horny tissues were preserved". He was "quite confident that the original organic material

The compositional profiles seem to confirm the original identification of the fossil specimen as tortoiseshell. Most of the amino acids are comparable in relative amounts with those recovered from the living material. The main exceptions are the increased proportions of aspartic acid and alanine and the reduction in glycine and tyrosine. These contrast with results from hair analyses, but can be matched with keratins derived from other tissues.

Although it is premature to draw any firm conclusions from these analyses, the differences between tortoiseshell and hair or wool are compatible with those between baleen and wool and hair. Fincham *et al.*⁶ suggested that the differences were a measure of the degree of calcification of the keratin, the proportion of proline increasing with mineralization. This indicates that tortoiseshell is fairly well calcified, which must have been a factor in its preservation.

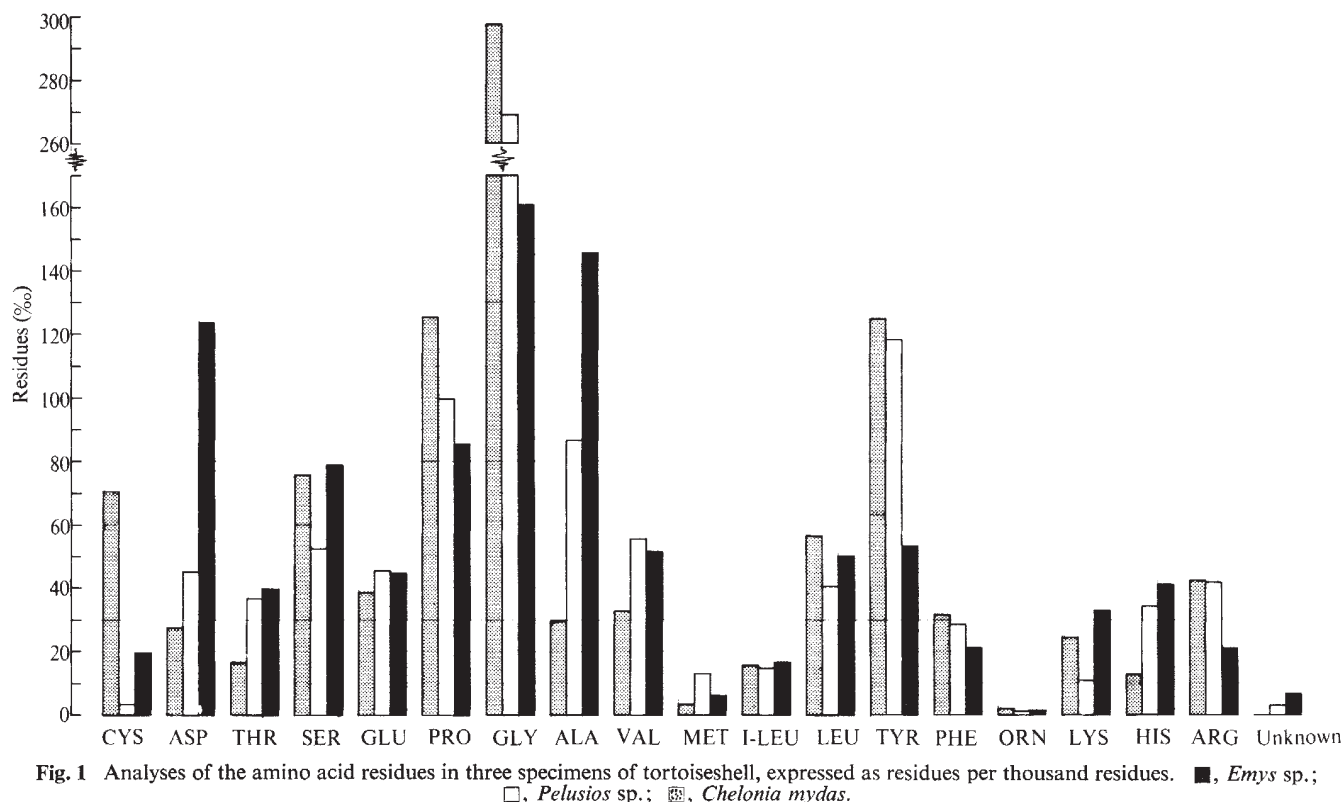


Fig. 1 Analyses of the amino acid residues in three specimens of tortoiseshell, expressed as residues per thousand residues. ■, *Emys* sp.; □, *Pelusios* sp.; ▨, *Chelonia mydas*.

has been completely replaced by calcite" (private communication).

During an excursion to the Isle of Wight, a fossil was found on the beach to the east of Whitecliff Bay, on the flats immediately west of Bembridge. The specimen measured approximately 4 × 1.5 cm and was translucent. It was identified as fossil tortoiseshell by one of us, although such material was unknown as fossil. Unfortunately it was not found *in situ*, but was mixed with bivalves belonging to the genus *Corbicula*, derived from the green marls of the Bembridge Marls⁴. The preservation in this deposit is somewhat unusual, in that even the colour banding of the bivalves still survives, and so it is the sort of deposit in which a material such as keratin might be expected to be preserved.

Analyses on various keratins have been restricted to hair, horn, nails, feathers and baleen⁵, and to date we have been unable to locate any accounts of the amino acid composition of tortoiseshell. Specimens of the tortoiseshell of two living genera, the marine *Chelonia* and the freshwater *Pelusios*, were analysed together with the fossil find, tentatively identified as *Emys*, the marsh-turtle. The separation and assay of the amino acids present in the hydrolysates of the specimens were made by means of a Technicon automatic amino acid analyser. The results obtained are given in Fig. 1.

The recognition that keratin can survive tens of millions of years, given suitable conditions of burial, could lead to further discoveries, enabling more palaeobiochemical analyses to be undertaken.

We thank Mr W. Martindale for the fossil specimen, Dr R. Moody of the Kingston Polytechnic for the living specimens and the Nuffield Foundation for a grant-in-aid.

L. B. HALSTEAD

Department of Biological Sciences,
University of Ife, Ile-Ife, Nigeria,
and Royal Dental School of London, London WC2

LILIANA WOOD

Department of Biochemistry,
Royal Dental School of London, London WC2

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BOOK REVIEWS

Reflexions on Mind

The Nature of Mind. By A. J. P. Kenny, H. C. Longuet-Higgins, J. R. Lucas, and C. H. Waddington. Pp. 155. (Edinburgh University: Edinburgh, 1972.) £1.50.

WE are told in the preface that the Gifford Committee decided to make a radical break with the past and have joint seminars or disputations on a theme by participants with widely different fields of scholarship. This certainly provided an entertaining experience for the audience, and would contrast with the feats of endurance required to listen to the lectures of some of the Gifford series. The published text, however, is less satisfactory. What is good in the repartee of debate needs much more editing than it received in this text. I do not refer to the verbal clashes such as "Kenny: I'd like to make two points about Waddington's paper. Firstly I don't think that freewill is the kind of thing he thinks it is and secondly I don't think that consciousness is the kind of thing that he thinks it is." That is good in-fighting, a tense introduction to his well reasoned attack. I refer to much tiresome repetition of some quite poor analogy or of some catchphrase. In places, it is like watching the skirmishing of some small and disorganized military conflict. The battle flares up now here, now there, and returns again for a re-fight of some previous skirmish. Nevertheless in the book there is much of great interest and for the most part it is easy reading. It is quite refreshing to experience the clash of argument and ideas of four experts.

It is unfortunate that in a book entitled *The Nature of Mind* there is confusion in usage of words. There are three terms in which there was much controversy as regards their meaning: (1) mind and mentality; (2) consciousness; (3) self-consciousness. Waddington regards as a sign of mind any purposive behaviour that can be interpreted as having self-perpetuation or species perpetuation. At one time he expressed panpsychic ideas, thinking there could be some consciousness even in a mug, but later was prepared to restrict it to animals with a nervous system. On the other hand, Kenny regards consciousness of animals as be-

yond doubt as, for example, in cats and dogs and for that reason criticizes Descartes in some way as "a great fool" and includes, of course, all others like myself who hold Cartesian views. Waddington, as a biologist, however, correctly points out that one cannot know for certain if animals are conscious. He states that the only justifiable attitude is that of agnosticism, but always giving animals the benefit of the doubt. In contrast to consciousness, Kenny reserves mind for human beings who are distinguished from animals by being language users—self-reflecting and rational. This, I would suggest, should be called self-consciousness. All seem agreed that self-consciousness is a purely human attribute.

There was some good fun and games with computers. But with Longuet-Higgins we do not get this slavish adulation—rather an analysis of weaknesses and deficiencies of the computer analogy with mind. We have entertaining conversations with computers, which of course disclose their linguistic deficiencies even with the best programming. Waddington twice raises the important question: Can you get a computer to examine the world and to formulate for itself appropriate goals?—only then can you justifiably attribute intelligence and rationality to it. There was no answer in the affirmative.

There is almost nothing specifically on the mind-brain problem, which may be expected from the deficient expertise of the group in the neural sciences and even in psychology. There is no reference at all to Feigl and the psycho-neural identity hypothesis. In general there are overtones of dualism, despite Kenny's flat statement that dualism is unacceptable. Thus dualism appears in efforts to define terms in which mind can be discussed. For example, language and intentions and decisions cannot be discussed in material terms. At the end of his excellent lecture, "The Failure of Reductionism," Longuet-Higgins states: "I have tried to show that neither neurophysiology nor behaviourist psychology will suffice for the construction of a science of the mind, because their concepts are not mental but physical. The initiative

must come from a more abstract level of description, such as logic or linguistics."

Dualism is also implied in the many quotations from Chomsky, which are discussed with approval. We hear again of faculties of the mind, the linguistic, the logical, the mathematical, which is a sign that the philosophies of materialist monism and behaviourism are in discard, which I note with approval. There are also signs of a return to Descartes in the revival of his concepts of the creative aspect of language—its innovational character, its potentiality to virtually an infinite variety of expression and its autonomous and coherent character.

There was much discussion, particularly in the lecture by Kenny, "To Mind via Syntax," of the role of language in consciousness. Non-linguistic conscious experience was played down, but Lucas made it a major theme in his lecture "Consciousness without Language." It was an appropriate counter to the tendency so often to exaggerate the linguistic content in thoughts. We must agree with Lucas that in the first place thoughts are about images—visual or acoustic in particular—and only secondarily do we try to express them, if we so desire, in language. In fact that is what language is for—to communicate our thoughts, our images, our intentions, our decisions. As Longuet-Higgins says, we do this in order to influence one another's mental processes, that is we have an active intention in communicating. Kenny objects in part, however, with the wise comment that "language is just as much a medium for ourselves to think our own thoughts in as it is a medium for the communication of thoughts to others." Finally Lucas raises the key problem of reflectiveness with its concomitants of self-assessment and self-criticism. What we may call self-consciousness—to be conscious that I am conscious or "*cognito me cogitare*" to cap Descartes's "*cogito ergo sum*."

Inevitably there is a full account of Chomsky's contributions. Of particular interest is Chomsky's postulate that even a newborn child has knowledge of a universal grammar as an innate

capacity. This permits the child to develop theories of language construction in his interpretation and performance. What is overlooked in this purely "mentalist" account is that there must be a neural counterpart to this linguistic performance. And we now know that the speech areas of the brain are built in intrauterine life beginning as soon as in the 20-week-old foetus. In these areas there must be built the highly specialized and unique neuronal machinery ready for use by the child postnatally. Chomsky is, I think, maintaining no more by his theory of innate knowledge than that this is coded in the specialized neural machinery of the speech areas, which of course is a result of genetic coding and of all the secondary instructions in the developmental process. This genetically built structure could of course be tuned in to any language. Animals lack the genetic coding for building such specialized brain areas. The most wonderful creation of the evolutionary process was in the development of the genetic coding for the construction of the linguistic areas of the brain.

The second series of these Gifford lectures is concerned with the development of mind. This provides the challenge to treat at length two great problems: the evolution of man in relation to linguistic evolution; the learning of a language by a child in contrast to the impoverished attempts by chimpanzees. The general consensus of the four symposiasts was that the self-consciousness of man was very intimately related to his linguistic abilities. Yet there was no mention of the remarkable discoveries of Sperry that, after brain bisection, the self-consciousness of the subject is related only to events in the linguistic hemisphere.

J. C. ECCLES

Wind Forces

Wind Forces in Engineering. By Peter Sachs. Pp. viii+392. (Pergamon: Oxford and New York, December 1972.) £12.

THE book is written "to bridge the widening gap between scientists and engineers in this subject". The writer is qualified by his experience and practice in the design of communication structures. Evidently the author's first major venture into print, it is a challenging book to write because it spans several different disciplines—climatology, meteorology, aerodynamics and structural engineering. This is perhaps why it has no competitors prominent on the market at present. There are good features to the book and a number of serious deficiencies. The arrangement and contents are generally well organized, the printing is satisfactory and the assembly of data generally scattered

far and wide is useful. There is an interesting section on wind loading on rotating antennae which has not perhaps reached the open literature before.

It is also the duty of the critic to draw attention to deficiencies. The recent references suggest that writing of the book ceased about 1967. Since then proceedings of two international conferences on wind forces have appeared (Ottawa, 1967; Tokyo, 1971). In a fast developing field this long time lag in the production dates the book and seriously devalues it as a bridge to contemporary thinking. The chapter on wind tunnel techniques perpetuates the myth that "in general wind tunnels developed for aircraft work are suitable for bluff models" (page 95)—at least if used to study wind forces on structures. In recent years it has been demonstrated time and time again that the wind shear and the turbulence in the Earth's boundary layer are not secondary but dominating influences. Structural shapes, stable in smooth flow, may be unstable in turbulent flow, and *vice versa*. Even the mean drag coefficient of a flat plate is affected by turbulence. Vortex shedding is universally a random phenomenon in turbulent flow, not only in the supercritical Reynolds number range as stated on page 162. The extent of this range is itself affected by turbulence. Throughout the chapter, modelling of turbulence and wind shear seem to be introduced as an afterthought and not as a primary modelling requirement. The summary of principal modelling parameters on page 109 makes no mention of either roughness length or turbulence scaling. They should be included. They are very important.

I was somewhat disappointed by the treatment of the statistical response to atmospheric turbulence; this leaves several lacunae. While there is reference to spatial correlation in chapter 2 dealing with wind structure, its important role in modifying the generalized force spectrum in spatially extended structures is not mentioned; the formulae derived are consequently incomplete. The determination of the peak values of response is dubious as is the method for adding variances. The chapter should be treated with caution.

While some relaxation of rigour must be permitted in a book of this nature, basic assumptions when stated should be correct. The treatment of Bernoulli's equation on page 2 could be improved in this regard. It is given without reference to the conditions under which it is obeyed and without the discussion of whether these conditions are met by the natural wind meeting a structure. The conditions for a Gaussian distribution discussed on page 29 are not dependent on stationarity nor on ergodicity as suggested.

Gust excitation is obviously not limited to along wind forcing only; it can, as with a suspension bridge, also be transverse to the flow direction. Vortex shedding, by the same token, can give rise not only to transverse forcing but also along wind, contrary to the statements on page 136. On page 102 there is the surprising suggestion that the power law velocity profile can be deduced from the logarithmic profile. The reference to "ultracritical Reynolds numbers" (page 252) instead of transcritical Reynolds numbers will raise aerodynamic eyebrows and lead to confusion.

The choice of units—feet/second and miles/hour—is unexpected in view of the adoption of the metric system in the UK; the statement that the unit of mass in the British system is the slug (page 358) is several years out of date. In conversion tables (for example A2.3) referring to speed in feet/second, m.p.h. and knots, makes no mention of metres/second. The standard unit of force, the Newton, is not defined. For those trying hard to adjust to the new units this would be an asset.

In summary I have serious reservations about this book. For the student its treatment of fundamentals is inadequate. For the practising engineer it is out of date, and contains an unacceptable number of errors of fact. Some of these errors are harmless, some may not be. Those who invest in this book should apply it cautiously.

A. G. DAVENPORT

Lions in Africa

The Serengeti Lion: a Study of Predator-Prey Relations. By G. B. Schaller. Pp. xiii+480. (University of Chicago: Chicago and London, 1972.) £5.65.

It is still a source of amazement to me that so little is known about the biology of the largest, most impressive and most conspicuously attractive animals. The large mammals of Africa have received the compliment of intensive study only in the past decade or two and for many of the most splendid creatures, for example the elephant, the buffalo and the rhinoceros, there is no comprehensive scientific account of their behaviour and ecology. An account of the king of beasts has had to wait until 1972. A book that gives, for the first time, a report of intensive and continuous study of the lion populations of the Serengeti could hardly fail to be fascinating and important: *The Serengeti Lion* is both of these but it has greater significance in that it reflects the renaissance of animal study in Africa. Past accounts of the lion are voluminous, of course, but they stem largely from the incidental experiences of naturalists or the tales of hunters. A notable exception is Guggisberg's

pioneering book of 1961, *Simba*, in which this painstaking scientist relates his studies of lions in the Nairobi National Park, carried out intermittently through a period of nearly ten years. Schaller's study was a continuous one, occupying almost the whole of three and a quarter years, and although Schaller complains of the inadequacies of his study, caused by its shortness, it is, in its intensity, a study that at last does justice to the supreme predator.

The social structure of a community of lions (such as the 2,000 or so in the ecological unit of the Serengeti) has to be discerned in the setting of a complex system of lion land-tenure. Some lions are resident and their focus is the pride. These lions are territorial but their range overlaps widely with neighbours. Other lions, both male and female, are nomads, but neither category signifies permanent status. Nomads may establish temporary territories and they have transitory contacts with a large number of other lions. Patterns of contact, tolerance, and familiarity emerged from Schaller's study but a question persisted that was profoundly important to the interpretation of behaviour, was not superficially anthropomorphic, and yet was tantalizingly elusive of answer: how many of these lions knew one another?

Fighting amongst lions was common, they often killed one another, and occasionally were cannibals. Territory holders did not always win an engagement with intruders.

The facts that Schaller has assembled on population dynamics and mortality in lions comprise most important new information about large predators. Most striking are the very heavy losses of cubs: 67% die. Abandonment, violence by adult lions, predation by hyaenas or leopards and starvation are the main causes of their deaths. Altogether the aggressive interactions between lions are seen to be an extremely potent force moulding their behaviour and survival pattern. Yet this aggression has marked survival value, for there are regular seasons and occasional years when lions have great difficulty in catching enough prey and many starve.

Schaller argues convincingly that food is the main factor controlling the lion population, yet he also presents compelling evidence for the importance of territory and adequate space. To read Schaller's findings, however, gives a strong impression that the lions are at too high a density. Many litters are abandoned and juvenile losses are high; the interval between litters is over twice as long as need be physiologically and some lionesses are barren; fatal encounters between adults are common, and so on. Undoubtedly, however, there are many periods when prey are superabundant and more lions could be supported. The reproductive activity

of lions is extremely labile and shows fascinating adaptation of physiological response to social and density factors.

Finally there is a wealth of new observation and invaluable statistics about the relation of predator and prey and the lion's hunting methods. In the Serengeti the zebra is the most frequent prey, far out of proportion to its abundance. I could discern no way in which its stripes avert the ultimate disaster of falling victim to the lion.

Facts about other predators, a general discussion of their social systems, and of the dynamics of predation, complete the assembled evidence and make this book a superbly rewarding outcome of the author's years of patient work. Schaller had his own reward in the work itself. In the days and nights of watching he became the familiar of the pride. . . . "I had empathy with their problems, I anticipated their future." He, at least, came to know who was who.

PETER JEWELL

Psychology of Industry

The Social Psychology of Work. By Michael Argyle. Pp. xii+291. (Allen Lane: London, October 1972.) £2.95.

MR ARGYLE has set himself the task of producing "a book that is both popular and scholarly". His particular criteria have been that it should be of use to a wide audience; and that all the assertions in it should be based on good evidence, with some of the main sources given.

In large measure he has succeeded. My guess is that the end result will appeal more to thinkers than to doers, but there is no harm in that. We have had an excess of packages of techniques in recent years, and it is refreshing to have someone of lively intellect and wit poking about, turning things over and having a good look, even if it is sometimes done in a rather unmethodical and idiosyncratic way. Bold, questioning managers will probably give Mr Argyle's book a bigger welcome than will the seekers after management gimmicks; and postgraduates in the behavioural sciences will perhaps think more of it than management students in polytechnics. But to all of them it has information and stimulation to offer. On the usual people—for example, Herzberg, McClelland, Maslow, Vroom—there are level-headed comments, and for once the Tavistock Institute has something useful written about it. Work in primitive societies is given passing but illuminating attention; and so are developments in modern societies (including Yugoslavia, Japan and Israel) which we in Britain do not often hear about.

Sometimes Mr Argyle says things which make one wonder about his second criterion. For example, he asserts that

for many years industrial psychologists concentrated their attention on the performance of manual skills, and that "no interest was taken in the more responsible and highly paid supervisors and managers". It would be more accurate to say that in the early days their attention was largely focused on operating (not merely manual) skills; and to say that their great interest in people in senior positions raised anxiety and was strongly discouraged. It is a pity that Mr Argyle has given further currency to myths which should by now have perished. C. S. Myers, who founded the National Institute of Industrial Psychology half a century ago (after investing much of his time and money in the Cambridge Psychological Laboratory, of which he became the first director), could have put him right on this. Myers is not mentioned in either his bibliography or his name index. Mr Argyle might, in a book on the social psychology of work, have given a thought to the fact that half of Myers's *Mind and Work*, published in 1920, was taken up by chapters on restriction of output, systems of payment, and industrial unrest.

In brief, the book is stimulating to read, but it has shortcomings, not least (despite the observations on the Tavistock Institute and some reference to the National Institute's joint consultation survey, and the work of a few individuals) in its neglect of relevant British work. American authors, with few exceptions, have been equally neglectful; but British authors have no excuse for following their example. I shall certainly recommend the book to postgraduate students (to borrow, not to buy, because its publication price is too high), but with reservations.

ALEC RODGER

X-ray Spectrochemistry

X-Rays, Electrons and Analytical Chemistry: Spectrochemical Analysis with X-Rays. By H. A. Liebhafsky, H. G. Pfeiffer, E. H. Winslow and P. D. Zemany. Collaborating editor: Sybil Small Liebhafsky. Pp. xii+566. (Wiley: New York and London, November 1972.) £10.45.

THIS book is a significant contribution to applied X-ray analysis as was the authors' 1960 book, *X-Ray Absorption and Emission in Analytical Chemistry*. The 1972 edition has approximately 50% new material including a chapter on X-ray diffraction and discussions on energy resolution, mathematical methods for calculating concentration and many good comments on practical solutions to X-ray analytical problems. For several years the senior author has been using the material for a graduate course in X-ray analysis at Texas A and M.

The book is characterized by realistic appraisals of the value of various X-ray techniques. Although the General Electric Laboratory made major contributions to the field of X-ray absorptiometry, the authors stress that emission applications are far more important and consequently reduced the discussion on absorptiometry—a technique with important but limited applications. Probably the most valuable chapter to the practising analyst is the one on general sample preparation, remedies and compensations. In the recent advertisements by the X-ray instrument companies, particularly those extolling energy dispersive techniques, the reader is led to believe that all problems can be solved in seconds with a semiconductor detector and a dedicated computer. In spite of all the advances in instrumentation, the authors' summary statement is still appropriate, "In most cases sample preparation and not the spectrograph system, if functioning properly, will limit the reliability of results." This point cannot be overly emphasized if the analyst wishes to avoid large systematic errors for many types of samples.

The authors also convey to the reader the importance of weighing the merits and limitations of X-ray techniques with other competitive analytical techniques such as atomic absorption and optical emission. Both analysts and instrument manufacturers must be aware of new developments in analytical chemistry that compete with their speciality. A recent example is the virtual takeover of electron probe X-ray spectrography by scanning electron microscopes having X-ray optical capability. The authors' paraphrase of the late President Truman is apropos in regard to X-ray methods, "If despite their manifest advantages they cannot withstand the heat of competition—they had better get out of the kitchen."

This new book is a welcome addition to the X-ray analyst's library and is recommended as a text for a course on X-ray methods of analysis as it includes X-ray diffraction and absorptiometry in addition to X-ray spectrography.

WILLIAM J. CAMPBELL

Algae Revisited

The Algae. By V. J. Chapman and D. J. Chapman. Pp. xiv+497. (Macmillan: London and Basingstoke, March 1973.) £6.95.

TEACHERS of phycology have need of an accurate, up-to-date account of the algae for student use in courses on these important plants. This new edition of *The Algae* by V. J. and D. J. Chapman does not, unfortunately, fill that need.

The later chapters include useful short accounts of marine and freshwater algal ecology, with examples of different situations and different

approaches to their study. The final chapter on algal physiology is so condensed that its usefulness is less certain, though it may serve as a lead-in to the research literature. In fact, with good reviews of algal ecology (Lewis, 1964; Round, 1965, for example), physiology and biochemistry (Stewart, 1973 for example) already available, what our students really need is a modern textbook on algal structure and reproduction, a latterday "Fritsch". It is precisely in this area that the book is less than satisfactory, with inaccuracies which vitiate its commendably wide coverage of organisms. (The advantage of this coverage is that students are more likely to find mention of an alga they are studying; the disadvantage is that the book tends to become a catalogue of thumb-nail sketches. In *Structure and Reproduction of the Algae* (1935, 1945), Fritsch took 1,750 closely packed pages to cover a wide range of plants and to include detailed accounts of the most important ones.)

In the taxonomic portion of the present book the annoying inaccuracies and imprecisions of language begin with the opening glossary and continue throughout the text. For example, in the glossary, the term "Frustule" is defined as "One half of a cell (Bacillariophyceae)", causing confusion with the main text (page 177), where the term is correctly given as synonymous with the total shell or wall of the diatom cell. Again, "Haptonema" is defined as "Flagella-like organ used for attachment to substrate (Haptophyceae)". Apart from problems over endings ("haptonema" is singular, "flagella" plural), this definition obscures the significant structural differences between haptonemata and flagella, and begs the question of haptonematal function, points also not adequately discussed in the text (page 172). Reading on, one is continually worried by similar inaccuracies, imprecise statements and misspellings (flagellates, accomodated, Bourcelly).

The arrangement of the taxonomic section is potentially confusing to students. There seems to be a desire to have chapters of about the same length, so that larger divisions (Chlorophyta, Phaeophyta, Rhodophyta) are arbitrarily split among several chapters, without uniform sub-headings, whereas smaller, not necessarily related, groups are put together (for example, chapter 6, Euglenophyta, Xanthophyta, Chloromonadophyta). Why not just have one chapter to each division? Incidentally, the page heading "Haptophyta" appears twice during the diatom section, when no such division is to be found in the book. Perhaps this is a subconscious feeling towards what I would have regarded as a correct decision to separate the Haptophyceae off from the

Chrysophyta as the division Haptophyta.

The Haptophyceae appear in this textbook for the first time in this edition, as do the Eustigmatophyceae, given as a class in the summary of classification at the beginning (page 7) but only as a paragraph within the Xanthophyceae in the main text (page 128). The important phycological reason for separating these last two classes, that motile cells of the former are unique in structure and less like those of the Xanthophyceae than the latter are like those of the Chrysophyceae and Phaeophyceae, is not mentioned. The other newcomers to this edition are the Euglenophyta, and minor inaccuracies and misconceptions again occur in the three pages devoted to them. The few drawings of euglenoids in this section are woefully inadequate and are not, as stated, "after Leedale". Three of the eight drawings are of "*Colacium caluum*" (misspelling for *C. calvum*, a species of doubtful validity); Fig. 6.1, g, is described as "*C. caluum*, euglenoid zoospore attached", a phrase I am still trying to interpret.

Mention of these drawings brings me to the low standard of many of the illustrations. Examples of sketchy misrepresentation begin with the blue-greens (for example, *Nostoc*, Fig. 2.8, shown with cells of irregular shape and size) and continue through the other groups. Perhaps the most amazing feature, however, is the total absence of photographs. The algae have been a rich area of cytological and ultrastructural research during the past 20 years, providing results of fundamental importance in comparative phycology and in the wider regions of basic biological information. This is for the most part ignored in the present book, and where ultrastructural studies are mentioned (diatom locomotion, eyespot structure, haptophycean scales, and so on) the significance of the observations is not adequately discussed. It seems regrettable that a new edition of a textbook on the algae published in 1973 can still include no electron micrographs; it is surely inadequate to have a few drawings of micrographs (for example, Figs 3.4, 8.7) which lack both the accuracy and impact of the real thing.

The algae are exciting plants, of absorbing interest for their fascinating structure, their range of reproductive systems, the diversity of their life-cycles, their physiological and biochemical variety, and for what study of these features has to tell us about the evolution and functioning of biological systems. The present book represents a missed chance to produce a stimulating student text combining studies of the algae by modern techniques with classical studies on morphology and life-histories.

GORDON F. LEEDALE

CORRESPONDENCE

Energy Crunch

SIR,—Your editorial remarks on "The Energy Crunch" (*Nature*, **243**, 485; 1973) is the latest of several attacks on the BBC's present science output. I work closely with the BBC without being part of it, so may I comment?

Your opinions about the comparative prospects for fission, fusion and solar energy are the conventional ones among experts, and you are right to air them. With some hedging, I should place my private bets much as you do. But I would not gamble the wellbeing of mankind on the assumption that we are necessarily right. Certainly I would not impugn, as you do, the motives behind television programmes that offer somewhat different opinions on the subject.

Times have changed and experts are no longer regarded as infallible. That is just as well, because the public would be misled much more seriously by too deferential treatment of science and technology than it is by occasional programmes with which some of us happen to disagree.

As for "balance", which seems to be the keyword in your editorial, what do you mean by it? Do you want equal broadcasting time for Freudians in psychology, for creationists in evolution studies, for anti-drifters in the earth sciences—much as the BBC in political programmes strives tediously to match a Labour man against a Tory? Presumably not, but that is because, looking around, you arrive at opinions about where the good science lies and which of the iconoclasts may turn out to be right.

The popularizer cannot avoid forming opinions either. Even just choosing a topic for a television programme is a value judgment. The quest for objectivity, in popularization as in research, is a subjective thing—a matter of an honest and inquiring disposition—rather than a ride down an asymptote towards some absolute truth.

Yours faithfully,

NIGEL CALDER

8 The Chase,
Furnace Green,
Crawley, Sussex RH10 6HW

USSR Jews

SIR,—I noticed lately in *Nature* (**243**, 313; **243**, 427; 1973) you shed some tears over the fate of Jewish scientists in USSR. Why Jews only?

Since the 1937 purges, intellectuals in USSR, specially in western republics, Ukraine, Byelorussia, Estonia, Karelia, Latvia, Lithuania, have been deported and executed on genocidal scale. Selective executions of "war criminals", of course, still occur with sickening regularity. Yet *Nature*, and the whole Western press, is concerned with the persecution of Jews only, not of people as a whole. If Jews are selected as a special people by Anglo-Saxons, was then Hitler that much wrong after all? Or is it different?

Yours faithfully,

V. SPAKOVSKIS

27 Shanklin Road,
Hill Lane,
Southampton

Obituary

Arthur Knyvett Totton

ARTHUR KNYVETT TOTTON, the well-known coelenterate taxonomist who worked for many years at the British Museum, died on January 12, 1973.

He was born on January 6, 1892, at Wallington, in Surrey, and was educated at Berkhamsted School. Wishing to prepare himself for a vacancy in the Natural History Museum he went in 1910 to the Royal College of Science. At the beginning of 1914 he joined the museum staff, becoming an associate worker in 1953 and, until he finally retired in 1967, his contributions to zoology were interrupted only by the two world wars.

As a student he was interested in the breadth of zoology, and the thoroughness with which he gained a wide knowledge of the subject and his early ability as an investigator were both characteristic. He attended some of Sedgwick's last classes, and his other teachers included E. J. Allen, W. T. Calman, A. D. Darbishire and C. Dobell. He

studied entomology under H. M. Lefroy and could have made it his career. The systematic study of vertebrates and invertebrates, and experimental embryology, he took under E. W. MacBride, and at the latter's suggestion he began his first research, appropriately enough using material which the trustees of the museum had handed to the college for description. The resulting paper on the development of the vertebral column in a teleost fish (1914) is critical and mature in style. It is significant that in his later work problems of development and homology are often discussed with great insight, and with an indelible interest in evolution.

Captain Totton, as he is remembered by colleagues, served with distinction in the 1914–18 war, and was commissioned in 1915 in the Duke of Cornwall's Light Infantry. He went to France in 1914 with the 28th Battalion of the London Regiment. He served at Ypres, the Somme District and Arras, and in 1916 received the Military Cross. He was severely wounded in the Somme in

1916, and was invalided out in 1918. He never gave in to the trying after-effects of his injuries, and at the outbreak of World War II he joined the Army Officers' Emergency Reserve, and took on the duties of ARP warden for the entire British Museum.

On returning to the museum in 1918 he was given sole charge of the coelenterate section. The broad range of his curatorial and other work is reflected in diverse publications extending from accounts of the *Antipatharia and Hydroids of the British "Terra Nova" Expedition* (1923, 1930) to notes on Australian corals (1952), and up to 1935 he contributed to *Zoological Record*. His major interest, however, lay with the siphonophores, among the most complex and exotic of organisms, and among the most challenging to the taxonomist. He set to work on them almost unaided and later said (1954) that it was the study of Bigelow's Albatross Report (1911) which first lured him to examine these animals and to build up an enormous collection of

them at the British Museum. His first major work on the group was in 1932, on the siphonophores of the Great Barrier Reef Expedition. Amongst many subsequent papers, the outstanding landmarks are the *Siphonophores of the Indian Ocean* (1954), the monograph on *Physalia* (1960) and the crowning achievement, the great *Synopsis* of 1965. Totton was without peer as a siphonophore specialist. His descriptions were based on the most exact study of great masses of material from sundry sources. He took endless pains to present a faithful account of the findings of his predecessors and to set them in just relation to his own. He wrote simple, vivid English, and his works are as readable as taxonomy could conceivably be. In several of his major works he attempted to present a simplified account for non-specialists along with the more technical parts.

His paedophore hypothesis (1960) has been influential among younger workers and his opinions are convincing because he distinguished carefully between "stimulating speculation on phylogeny" and "descriptive matter", although even he thought that it was no easy task to reconstruct the zigzag course of evolution in this group. First and foremost, however, he was a taxonomist, to whom a library of specimens was as essential as access to books. The examination of plankton samples (many from Discovery collections) and the analysis of fragmented specimens involved no little labour, and he was fortunate in the help given over many years by his assistant Mr Ernest White, for whom he expressed his esteem by conferring his name on a new species. Similar tributes were paid to other colleagues, and Totton's nomenclature has a zest of its own, of which anyone who knows of his lifelong

interest in the Scout movement will find *Lensia lelouveteau* a good example.

His essential and very exact taxonomic groundwork has made it possible to follow the movements of water masses in the sea by studying the distribution of siphonophore species, as, for example, in Dr J. H. Fraser's work in the Northeast Atlantic. Such water movements have very profound effects on fisheries.

Opportunities to work with living siphonophores afforded him joyful delight, and in the tradition of great naturalists he conveyed his enthusiasm to all who worked with him. His writings continually bring out the need to observe, or to revise facts, and are never for a moment dull. All beginners, he maintained, should see living material, and today all zoologists would agree with him. He himself had few such opportunities in earlier days, although in 1930 he visited the Caribbean on HMS Rodney. In 1955, following Haeckel's geographical intuition, he went to Arrecife with G. O. Mackie to work on *Physalia*, and from 1949 he made visits to Villefranche year by year so that the Station Zoologique became a second home.

Totton was the least stuffy of men. He could utter outrageously reactionary views but this was often done mischievously to provoke a response, and arguments often ended in his yielding his position in an apparent state of apoplectic self-restraint, somehow gratifying to his antagonist. He had remarkable ability to enlist the efforts of others on behalf of his projects, combining the qualities of Ancient Mariner, Svengali, and Portuguese Man-of-War. His friends will remember his sardonic humour, his innate romanticism, his warmth and his *esprit*.

Erratum

IN the article "Subcutaneous Growth of Human Tumours in Mice" by C. R. Franks, F. T. Perkins and J. Thornton Holmes (*Nature*, 243, 91; 1973) paragraph 3, line 3, should read "and 100 $\mu\text{g ml}^{-1}$ streptomycin", instead of "100 mg streptomycin".

Reports and Publications

not included in the Monthly Books Supplement

Great Britain and Ireland

Institution of Gas Engineers. Communications. No. 867: Presidential Address, 109th Annual General Meeting, London, 16/18 May 1972. By J. A. Buckley. Pp. 17. 75p. No. 868: Natural Gas as a Factor in Air Pollution Control. By Dr. Alice Garnett and P. Read. Pp. 23. 75p. No. 869: The International Consultancy Service: An Economic and Social Force in Global Gas Industry. By C. E. Mills. Pp. 17. 75p. No. 870: The Glenmavis Natural Gas Liquefaction and Storage Facility—Experiences in its Design, Construction and Commissioning. By A. B. Garbutt and L. Thompson. Pp. 36. 75p. No. 871: Experience Gained in the Commissioning of the Ling Storage Installation in Stuttgart. By Dr. Heinz Berge and Jürgen Poll. Pp. 17. 75p. No. 872: Long Distance Liquid Natural Gas Pipelines. By Prof. G. Walker, Prof. D. M. Coulter and Prof. D. H. Norrie. Pp. 19. 75p. No. 873: Some Design Considerations and Operational Experience with UK Gas Compressor Stations. By A. Cleveland and D. A. Young. Pp. 31. 75p. No. 774: Converting Customer Service. By B. C. Smith and H. B. Healy. Pp. 22. 75p. No. 875: Marketing—Southern Style. By J. F. Doran. Pp. 29. No. 876: Gas Control with an On-Line Computer. By K. R. Brookes and A. W. Coles. Pp. 26. No. 766: Change and Exchange in International Energy Supply. By Carol V. Kroeger. Pp. 24. 109th Annual General Meeting, London, 1972—Discussions. Pp. 163. £1. (London: The Institution of Gas Engineers, 1973.) [262]

Other Countries

Bureau International des Poids et Mesures. Le Système International d'Unités (SI). 2e Edition. Pp. 40. (Sevres, France: Bureau International des Poids et Mesures, 1973.) [262]
European Organization for Nuclear Research, CERN. CERN 73-2: A Split Field Magnet Geometry for Program: NICOLE. By M. Metcalf, M. Regler and C. Broll. Pp. 33. (Geneva: CERN, 1973.) [262]
En la Marcha Universitaria de Avance, Extension y Ascenso. Por Dr. Jose Joaquin Izquierdo. Pp. 48. (Mexico, DF: Dr. Jose Joaquin Izquierdo, Calle de Colima numero 367, 1972.) [262]

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